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SECOND EDITION

CASE FILES®
Family Medicine

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DEDICATION

To my wonderful partners at the CHRISTUS Southwest Community Health Clinic including our leaders Sister Rosanne Popp, MD and Tyrone Springs, DDS; the excellent nurse practitioners Bernie, Cornell, Carlisa, and Kathy; and my phenomenal sonographer Patty—you and your associates are the everyday heroes providing medical care to the underserved each day.

— ECT

To Cal, Casey, and Heather.

— DB

To the students, residents, faculty and patients of EVMS: the best teachers I could ever have.
And to May and Sean: for their infinite patience and love.

— BB

To my loving parents,
whose sincerity, sacrifice, and hard work have made my efforts possible.

— BR

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PREFACE

We appreciate all the kind remarks and suggestions from the many medical students over the past 3 years. Your positive reception has been an incredible encouragement, especially in light of the short life of the *Case Files* series. In this second edition of *Case Files: Family Medicine*, the basic format of the book has been retained. Improvements were made in updating many of the chapters. New cases include back pain, movement disorders and developmental disorders. We reviewed the clinical scenarios with the intent of improving them; however, their "real-life" presentations patterned after actual clinical experience were accurate and instructive. The multiple-choice questions have been carefully reviewed and rewritten to ensure that they comply with the National Board and USMLE format. Through this second edition, we hope that the reader will continue to enjoy learning diagnosis and management through the simulated clinical cases. It certainly is a privilege to be teachers for so many students, and it is with humility that we present this edition.

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The curriculum that evolved into the ideas for this series was inspired by two talented and forthright students, Philbert Yau and Chuck Rosipal, who have since graduated from medical school. It has been a pleasure to work with Dr. Don Briscoe, a brilliant, compassionate, and dedicated teacher and leader, and Dr. Bruce Britton, who is an excellent teacher and communicator. Likewise, it has been a pleasure to work with Dr. Bal Reddy who is energetic and passionate about medical education. I am greatly indebted to my editor, Catherine Johnson, whose exuberance, experience, and vision helped to shape this series. I appreciate McGraw-Hill's believing in the concept of teaching through clinical cases, I am also grateful to Catherine Saggese for her excellent production expertise, and Cindy Yoo for her wonderful editing. I cherish the ever-organized and precise Gita Raman, senior project manager, whose friendship and talent I greatly value; she keeps me focused, and nurtures each of my books from manuscript to print. I appreciate Marla Buffington who adds warmth to the residency program. Three medical students, Molly Dudley, Lauren Laroche, and Patrick Beeman, helped to read through the manuscript and verify the appropriateness of the content, and to them I am very grateful. To Patrick, I owe special thanks for his meticulous reading, thoughtful comments, and expert critique of the questions and explanations. Patrick would like to thank his wife Christine for supporting his many extracurricular activities and Dr. Edmund Pellegrino for his indefatigable and inspiring example of what a doctor should be. At the Methodist Hospital, I thank Drs. Marc Boom, Dirk Sostman, Judy Paukert, Alan Kaplan, and Ms. Ayse McCracken and Mr. Reggie Abraham for their phenomenal encouragement. At St. Joseph Medical Center, I am appreciative of Mr. Philip Robinson, Mr. Patrick Mathews, Ms. Laura Fortin, Ms. Marivel Lozano, and Dr. Thomas Taylor for their leadership and support. Most of all, I appreciate my ever-loving wife Terri, and four wonderful children, Andy, Michael, Allison, and Christina for their patience, encouragement, and understanding.

Eugene C. Toy, MD

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INTRODUCTION

Mastering the cognitive knowledge within a field such as family medicine is a formidable task. It is even more difficult to draw on that knowledge, procure and filter through the clinical and laboratory data, develop a differential diagnosis, and, finally, to form a rational treatment plan. To gain these skills, the student often learns best at the bedside, guided and instructed by experienced teachers, and inspired toward self-directed, diligent reading. Clearly, there is no replacement for education at the bedside. Unfortunately, clinical situations usually do not encompass the breadth of the specialty. Perhaps the best alternative is a carefully crafted patient case designed to stimulate the clinical approach and decision making. In an attempt to achieve that goal, we have constructed a collection of clinical vignettes to teach diagnostic or therapeutic approaches that are relevant to family medicine. Most importantly, the explanations for the cases emphasize the mechanisms and underlying principles, rather than merely rote questions and answers.

This book is organized for versatility: to allow the student "in a rush" to go quickly through the scenarios and check the corresponding answers, as well as enable the student who wants thought-provoking explanations to take a slower path. The answers are arranged from simple to complex: a summary of the pertinent points, the bare answers, an analysis of the case, an approach to the topic, a comprehension test at the end for reinforcement and emphasis, and a list of resources for further reading. The clinical vignettes are purposely placed in random order to simulate the way that real patients present to the practitioner. Section III includes a listing of cases to aid the student who desires to test his/her knowledge of a certain area, or to review a topic including basic definitions. Finally, we intentionally did not primarily use a multiple choice question (MCQ) format because clues (or distractions) are not available in the real world. Nevertheless, several MCQs are included at the end of each scenario to reinforce concepts or introduce related topics.

HOW TO GET THE MOST OUT OF THIS BOOK

Each case is designed to simulate a patient encounter with open-ended questions. At times, the patient's complaint is different from the most concerning issue, and sometimes extraneous information is given. The answers are organized with four different parts.

PART I

1. The **Summary** identifies the salient aspects of the case, filtering out the extraneous information. The student should formulate his/her summary from the case before looking at the answers. A comparison to the summation in the answer will help to improve one's ability to focus on the important data, while appropriately discarding the irrelevant information, a fundamental skill in clinical problem-solving.
2. A **straightforward** answer is given to each open-ended question.
3. The **Analysis of the Case,** which is comprised of two parts:
   a. **Objectives** of the Case: A listing of the two or three main principles that are crucial for a practitioner in managing the patient. Again, the student is challenged to make educated "guesses" about the objectives of the case upon initial review of the case scenario, which help to sharpen his/her clinical and analytical skills.
   b. **Considerations:** A discussion of the relevant points and a brief approach to the specific patient.

PART II

The **Approach to the Disease Process,** which has two distinct parts:

a. **Definitions or pathophysiology:** Terminology or basic science correlates that are pertinent to the disease process.

b. **Clinical Approach:** A discussion of the approach to the clinical problem in general, including tables, figures, and algorithms.

PART III

The **Comprehension Questions** for each case is composed of several multiple-choice questions that either reinforce the material or introduce new and related concepts. Questions about material not found in the text have explanations in the answers.

PART IV

Clinical Pearls are a listing of several clinically important points that summarize the text, and allow for easy review of the material, such as before an examination.

SECTION I

How to Approach Clinical Problems

Part 1. Approach to the Patient

Applying "book learning" to a specific clinical situation is one the most challenging tasks in medicine. To do so, the clinician must not only retain information, organize facts, and recall large amounts of data but also apply all of this to the patient. The purpose of this text is to facilitate this process.

The first step involves gathering information, also known as establishing the database. This includes taking the history, performing the physical examination, and obtaining selective laboratory examinations, special studies, and/or imaging tests. Sensitivity and respect should always be exercised during the interview of patients. A good clinician also knows how to ask the same question in several different ways, using different terminology. For example, patients may deny having "congestive heart failure" but will answer affirmatively to being treated for "fluid on the lungs."

Clinical Pearl

➤ The history is usually the single most important tool in obtaining a diagnosis. The art of seeking this information in a nonjudgmental, sensitive, and thorough manner cannot be overemphasized.

HISTORY

1. Basic information
   a. Age: Some conditions are more common at certain ages; for instance, chest pain in an elderly patient is more worrisome for coronary artery disease than the same complaint in a teenager.
   b. Gender: Some disorders are more common in men, such as abdominal aortic aneurysms. In contrast, women more commonly have autoimmune problems, such as chronic idiopathic thrombocytopenic purpura or systemic lupus erythematosus. Also, the possibility of pregnancy must be considered in any woman of child-bearing age.
   c. Ethnicity: Some disease processes are more common in certain ethnic groups (such as type 2 diabetes mellitus in the Hispanic population).

Clinical Pearl

➤ Family Medicine illustrates the importance of longitudinal care; that is, seeing the patient in various phases and stages of life.

2. Chief Complaint: What is it that brought the patient into the hospital? Has there been a change in a chronic or recurring condition or is this a

completely new problem? The duration and character of the complaint, associated symptoms, and exacerbating/relieving factors should be recorded. The chief complaint engenders a differential diagnosis, and the possible etiologies should be explored by further inquiry.

Clinical Pearl

➤ The first line of any presentation should include *Age, Ethnicity, Gender, Marital Status, and Chief Complaint.* Example: A 32-year-old married White male complains of lower abdominal pain of 8-hour duration.

3. Past Medical History
   a. Major illnesses such as hypertension, diabetes, reactive airway disease, congestive heart failure, angina, or stroke should be detailed.
      i. Age of onset, severity, end-organ involvement.
      ii. Medications taken for the particular illness, including any recent changes to medications and reason for the change(s).
      iii. Last evaluation of the condition (eg, When was the last stress test or cardiac catheterization performed in the patient with angina?)
      iv. Which physician or clinic is following the patient for the disorder?
   b. Minor illnesses such as recent upper respiratory infections.
   c. Hospitalizations, no matter how trivial, should be queried.
4. Past Surgical History: Date and type of procedure performed, indication, and outcome. Laparoscopy versus laparotomy should be distinguished. Surgeon and hospital name/location should be listed. This information should be correlated with the surgical scars on the patient's body. Any complications should be delineated including anesthetic complications, difficult intubations, and so on.
5. Allergies: Reactions to medications should be recorded, including severity and temporal relationship to medication. Immediate hypersensitivity should be distinguished from an adverse reaction.
6. Medications: A list of medications, dosage, route of administration and frequency, and duration of use should be developed. Prescription, over-the-counter, and herbal remedies are all relevant. If the patient is currently taking antibiotics, it is important to note what type of infection is being treated.
7. Immunization History: Vaccination and prevention of disease is a principal goal of the family physician; hence, recording the immunizations received including dates, age, route, and adverse reactions, if any, is critical.
8. Screening History: Cost-effective surveillance for common diseases or malignancy is another cornerstone responsibility of the family physician. An organized record-keeping is important to a time-efficient approach to this area.
9. Social History: Occupation, marital status, family support, and tendencies toward depression or anxiety are important. Use or abuse of illicit drugs,

tobacco, or alcohol should also be recorded. Social history, including marital stressors, sexual dysfunction, and sexual preference, are of importance.

10. Family History: Many major medical problems are genetically transmitted (eg, hemophilia, sickle cell disease). In addition, a family history of conditions such as breast cancer and ischemic heart disease can be a risk factor for the development of these diseases.
11. Review of Systems: A systematic review should be performed but focused on the life-threatening and the more common diseases. For example, in a young man with a testicular mass, trauma to the area, weight loss, and infectious symptoms are important to note. In an elderly woman with generalized weakness, symptoms suggestive of cardiac disease should be elicited, such as chest pain, shortness of breath, fatigue, or palpitations.

PHYSICAL EXAMINATION

1. General Appearance: Mental status, alert versus obtunded, anxious, in pain, in distress, interaction with other family members, and with examiner.
2. Vital Signs: Record the temperature, blood pressure, heart rate, and respiratory rate. An oxygen saturation is useful in patients with respiratory symptoms. Height and weight are often placed here with a body mass index calculated (weight in kg/height in m squared = kg/m^2).
3. Head and Neck Examination: Evidence of trauma, tumors, facial edema, goiter and thyroid nodules, and carotid bruits should be sought. In patients with altered mental status or a head injury, pupillary size, symmetry, and reactivity are important. Mucous membranes should be inspected for pallor, jaundice, and evidence of dehydration. Cervical and supraclavicular nodes should be palpated.
4. Breast Examination: Inspection for symmetry and skin or nipple retraction, as well as palpation for masses. The nipple should be assessed for discharge, and the axillary and supraclavicular regions should be examined.
5. Cardiac Examination: The point of maximal impulse (PMI) should be ascertained, and the heart auscultated at the apex and base. It is important to note whether the auscultated rhythm is regular or irregular. Heart sounds (including S_3 and S_4), murmurs, clicks, and rubs should be characterized. Systolic flow murmurs are fairly common as a result of the increased cardiac output, but significant diastolic murmurs are unusual.
6. Pulmonary Examination: The lung fields should be examined systematically and thoroughly. Strid or, wheezes, rales, and rhonchi should be recorded. The clinician should also search for evidence of consolidation (bronchial breath sounds, egophony) and increased work of breathing (retractions, abdominal breathing, accessory muscle use).
7. Abdominal Examination: The abdomen should be inspected for scars, distension, masses, and discoloration. For instance, the Grey-Turner sign of bruising at the flank areas may indicate intraabdominal or retroperitoneal hemorrhage. Auscultation should identify normal versus high-pitched and

hyperactive versus hypoactive bowel sounds. The abdomen should be percussed for the presence of shifting dullness (indicating ascites). Then careful palpation should begin away from the area of pain and progress to include the whole abdomen to assess for tenderness, masses, organomegaly (ie, spleen or liver), and peritoneal signs. Guarding and whether it is voluntary or involuntary should be noted.

8. Back and Spine Examination: The back should be assessed for symmetry, tenderness, and masses. The flank regions particularly are important to assess for pain on percussion that may indicate renal disease.
9. Genital Examination
   a. Female: The external genitalia should be inspected, then the speculum used to visualize the cervix and vagina. A bimanual examination should attempt to elicit cervical motion tenderness, uterine size, and ovarian masses or tenderness.
   b. Male: The penis should be examined for hypospadias, lesions, and discharge. The scrotum should be palpated for tenderness and masses. If a mass is present, it can be transilluminated to distinguish between solid and cystic masses. The groin region should be carefully palpated for bulging (hernias) upon rest and provocation (coughing, standing).
   c. Rectal examination: A rectal examination will reveal masses in the posterior pelvis and may identify gross or occult blood in the stool. In females, nodularity and tenderness in the uterosacral ligament may be signs of endometriosis. The posterior uterus and palpable masses in the cul-de-sac may be identified by rectal examination. In the male, the prostate gland should be palpated for tenderness, nodularity, and enlargement.
10. Extremities/Skin: The presence of joint effusions, tenderness, rashes, edema, and cyanosis should be recorded. It is also important to note capillary refill and peripheral pulses.
11. Neurologic Examination: Patients who present with neurologic complaints require a thorough assessment including mental status, cranial nerves, strength, sensation, reflexes, and cerebellar function.

Clinical Pearl

➤ A thorough understanding of functional anatomy is important to optimally interpret the physical examination findings.

12. Laboratory Assessment Depends on the Circumstances.
   a. CBC, or complete blood count, can assess for anemia, leukocytosis (infection), and thrombocytopenia.
   b. Basic metabolic panel: electrolytes, glucose, BUN (blood urea nitrogen), and creatinine (renal function).

c. Urinalysis and/or urine culture to assess for hematuria, pyuria, or bacteruria. A pregnancy test is important in women of child-bearing age.
d. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, alkaline phosphatase for liver function; amylase and lipase to evaluate the pancreas.
e. Cardiac markers (creatine kinase myocardial band [CK-MB], troponin, myoglobin) if coronary artery disease or other cardiac dysfunction is suspected.
f. Drug levels such as acetaminophen level **in possible overdoses.**
g. Arterial blood gas measurements give information about oxygenation, but also carbon dioxide and pH readings.

13. Diagnostic Adjuncts
a. Electrocardiogram if cardiac ischemia, dysrhythmia, or other cardiac dysfunction is suspected.
b. Ultrasound examination is useful in evaluating pelvic processes in female patients (eg, pelvic inflammatory disease, tuboovarian abscess) and in diagnosing gall stones and other gallbladder disease. With the addition of color-flow Doppler, deep venous thrombosis and ovarian or testicular torsion can be detected.
c. Computed tomography (CT) is useful in assessing the brain for masses, bleeding, strokes, skull fractures. CTs of the chest can evaluate for masses, fluid collections, aortic dissections, and pulmonary emboli. Abdominal CTs can detect infection (abscess, appendicitis, diverticulitis), masses, aortic aneurysms, and ureteral stones.
d. Magnetic resonance imaging (MRI) helps to identifiy soft tissue planes very well. In the emergency department setting, this is most commonly used to rule out spinal cord compression, cauda equina syndrome, and epidural abscess or hematoma.
e. Screening tests: Fasting lipid panel can demonstrate the cholesterol level, including the low-density lipoprotein (LDL) levels, which have prognostic significance in coronary heart disease; fasting glucose and thyroid tests may be important; in many centers, dual-energy x-ray absorptiometry (DEXA) is the test of choice to monitor bone mineral density; the mammogram is the examination of choice to assess for subclinical breast cancer; the double-contrast barium enema and colonoscopy are used to detect colonic polyps or malignancy.

Part 2. Approach to Clinical Problem Solving

CLASSIC CLINICAL PROBLEM SOLVING

There are typically four distinct steps that the family physician undertakes to systematically solve most clinical problems:

1. Making the diagnosis
2. Assessing the severity of the disease
3. Treating based on the stage of the disease
4. Following the patient's response to the treatment

Making the Diagnosis

This is achieved by carefully evaluating the patient, analyzing the information, assessing risk factors, and developing a list of possible diagnoses (the differential). Usually a long list of possible diagnoses can be pared down to a few of the most likely or most serious ones, based on the clinician's knowledge, experience, and selective testing. For example, a patient who complains of upper abdominal pain and has a history of nonsteroidal anti-inflammatory drug (NSAID) use may have peptic ulcer disease; another patient who has abdominal pain, fatty food intolerance, and abdominal bloating may have cholelithiasis. Yet another individual with a 1-day history of periumbilical pain that now localizes to the right lower quadrant may have acute appendicitis.

Clinical Pearl

➤ The first step in clinical problem solving is making the diagnosis.

Assessing the Severity of the Disease

After establishing the diagnosis, the next step is to characterize the severity of the disease process; in other words, to describe "how bad" the disease is. This may be as simple as determining whether a patient is "sick" or "not sick." Is the patient with a urinary tract infection septic or stable for outpatient therapy? In other cases, a more formal staging may be used. For example, cancer staging is used for the strict assessment of extent of malignancy.

Clinical Pearl

➤ The second step in clinical problem solving is to establish the severity or stage of disease. This usually impacts the treatment and/or prognosis.

Treating Based on Stage

Many illnesses are characterized by stage or severity because this affects prognosis and treatment. As an example, a formerly healthy young man with pneumonia and no respiratory distress may be treated with oral antibiotics at home. An older person with emphysema and pneumonia would probably be

admitted to the hospital for IV antibiotics. A patient with pneumonia and respiratory failure would likely be intubated and admitted to the intensive care unit for further treatment.

Clinical Pearl

➤ The third step in clinical problem solving is tailoring the treatment to fit the severity or "stage" of the disease.

Following the Response to Treatment

The final step in the approach to disease is to follow the patient's response to the therapy. Some responses are clinical, such as improvement (or lack of improvement) in a patient's pain. Other responses may be followed by testing (eg, monitoring the anion gap in a patient with diabetic ketoacidosis). The clinician must be prepared to know what to do if the patient does not respond as expected. Is the next step to treat again, to reassess the diagnosis, or to follow-up with another more specific test?

Clinical Pearl

➤ The fourth step in clinical problem solving is to monitor treatment response or efficacy. This may be measured in different ways—symptomatically or based on physical examination or other testing. For the emergency physician, the vital signs, oxygenation, urine output, and mental status are the key parameters.

Part 3. Approach to Reading

The clinical problem-oriented approach to reading is different from the classic "systematic" research of a disease. Patients rarely present with a clear diagnosis; hence, the student must become skilled in applying textbook information to the clinical scenario. Because reading with a purpose improves the retention of information, the student should read with the goal of answering specific questions. There are several fundamental questions that facilitate clinical thinking. These are:

1. What is the most likely diagnosis?
2. How would you confirm the diagnosis?
3. What should be your next step?
4. What is the best screening strategy in this situation?

5. What are the risk factors for this condition?
6. What are the complications associated with the disease process?
7. What is the best therapy?

Clinical Pearl

➤ Reading with the purpose of answering the seven fundamental clinical questions improves retention of information and facilitates the application of "book knowledge" to "clinical knowledge."

WHAT IS THE MOST LIKELY DIAGNOSIS?

The method of establishing the diagnosis was discussed in the previous section. One way of determining the most likely diagnosis is to develop standard "approaches" to common clinical problems. It is helpful to understand the most common causes of various presentations, such as "the worst headache of the patient's life is worrisome for a subarachnoid hemorrhage" (see the Clinical Pearls at end of each case).

The clinical scenario would be something such as:

A 38-year-old woman is noted to have a 2-day history of unilateral, throbbing headache with photophobia. What is the most likely diagnosis?

With no other information to go on, the student would note that this woman has a unilateral headache with photophobia. Using the "most common cause" information, the student would make an educated guess that the patient has a migraine headache. If instead the patient is noted to have "the worst headache of her life," the student would use the Clinical Pearl

The worst headache of the patient's life is worrisome for a subarachnoid hemorrhage.

Clinical Pearl

➤ The more common cause of a unilateral, throbbing headache with photophobia is a migraine, but the main concern is subarachnoid hemorrhage. If the patient describes this as "the worst headache of her life," the concern for a subarachnoid bleed is increased.

HOW WOULD YOU CONFIRM THE DIAGNOSIS?

In the scenario above, the woman with "the worst headache" is suspected of having a subarachnoid hemorrhage. This diagnosis could be confirmed by a

CT scan of the head and/or lumbar puncture. The student should learn the limitations of various diagnostic tests, especially when used early in a disease process. The lumbar puncture (LP) **showing xanthochromia (red blood cells) is the "gold standard" test for diagnosing subarachnoid hemorrhage, but it may be negative early in the disease course.**

What should be your next step? This question is difficult because the next step has many possibilities; the answer may be to obtain more diagnostic information, stage the illness, or introduce therapy. It is often a more challenging question than "What is the most likely diagnosis?" because there may be insufficient information to make a diagnosis and the next step may be to pursue more diagnostic information. Another possibility is that there is enough information for a probable diagnosis, and the next step is to stage the disease. Finally, the most appropriate answer may be to treat. Hence, from clinical data, a judgment needs to be rendered regarding how far along one is on the road of:

1. Make a diagnosis → 2. Stage the disease →
3. Treat based on stage → 4. Follow response

Frequently, the student is taught "to regurgitate" the same information that someone has written about a particular disease, but is not skilled at identifying the next step. This talent is learned optimally at the bedside, in a supportive environment, with freedom to make educated guesses, and with constructive feedback. A sample scenario might describe a student's thought process as follows:

1. MAKE THE DIAGNOSIS: "Based on the information I have, I believe that the patient has a small bowel obstruction from adhesive disease *because* he presents with nausea and vomiting, abdominal distension, and high-pitched hyperactive bowel sounds, and has dilated loops of small bowel on x-ray."
2. STAGE THE DISEASE: "I don't believe that this is severe disease as he does not have fever, evidence of sepsis, intractable pain, peritoneal signs, or leukocytosis."
3. TREAT BASED ON STAGE: "Therefore, my next step is to treat with nothing per mouth, nasogastric (NG) tube drainage, IV fluids, and observation."
4. FOLLOW RESPONSE: "I want to follow the treatment by assessing his pain (I will ask him to rate the pain on a scale of 1 to 10 every day), his bowel function (I will ask whether he has had nausea, or vomiting, or passed flatus), his temperature, abdominal examination, serum bicarbonate (for metabolic acidemia), and white blood cell count, and then reassess him in 48 hours."

In a similar patient, when the clinical presentation is unclear, perhaps the best "next step" may be diagnostic such as an oral contrast radiologic study to assess for bowel obstruction.

Clinical Pearl

➤ Usually, the vague query, "What is your next step?" is the most difficult question because the answer may be diagnostic, staging, or therapeutic.

WHAT IS THE BEST SCREENING STRATEGY IN THIS SITUATION?

A major role of the family physician is screening for common and/or dangerous conditions where there may be interventions to alleviate disease. Cost-effectiveness, ease of the screening modality, wide availability, and presence of intervention are some of the important issues. The age, gender, and risk factors for the disease process in question play roles. In general, age is one of the most important risk factors for cancer. For instance, with breast cancer, an annual mammography is recommended in women older than age 50 years. This imaging technique is widely available, inexpensive, safe, decreases mortality, and is cost-effective.

WHAT ARE THE RISK FACTORS FOR THIS PROCESS?

Understanding the risk factors helps the practitioner to establish a diagnosis and to determine how to interpret tests. For example, understanding risk-factor analysis may help in the management of a 55-year-old woman with anemia. If the patient has risk factors for endometrial cancer (such as diabetes, hypertension, anovulation) and complains of postmenopausal bleeding, she likely has endometrial carcinoma and should have an endometrial biopsy. Otherwise, occult colonic bleeding is a common etiology. If she takes NSAIDs or aspirin, then peptic ulcer disease is the most likely cause.

Clinical Pearl

➤ Being able to assess risk factors helps to guide testing and develop the differential diagnosis.

WHAT ARE THE COMPLICATIONS TO THIS PROCESS?

Clinicians must be cognizant of the complications of a disease, so that they will understand how to follow and monitor the patient. Sometimes the student has to make the diagnosis from clinical clues and then apply his/her knowledge of the consequences of the pathologic process. For example, "A 26-year-old male complains of right lower-extremity swelling and pain after a trans-Atlantic flight"

and his Doppler ultrasound reveals a deep vein thrombosis. Complications of this process include pulmonary embolism (PE). Understanding the types of consequences also helps the clinician to be aware of the dangers to a patient. If the patient has any symptoms consistent with a PE, a ventilation–perfusion scan or CT scan angiographic imaging of the chest may be necessary.

WHAT IS THE BEST THERAPY?

To answer this question, not only does the clinician need to reach the correct diagnosis and assess the severity of the condition, but (s)he must also weigh the situation to determine the appropriate intervention. For the student, knowing exact dosages is not as important as understanding the best medication, route of delivery, mechanism of action, and possible complications. It is important for the student to be able to verbalize the diagnosis and the rationale for the therapy.

Clinical Pearl

➤ Therapy should be logical and based on the severity of disease and the specific diagnosis. An exception to this rule is in an emergent situation, such as respiratory failure or shock, when the patient needs treatment even as the etiology is being investigated.

Summary

1. There is no replacement for a meticulous history and physical examination.
2. There are four steps in the clinical approach to the family medicine patient: making the diagnosis; assessing severity; treating based on severity; and following response.
3. There are seven questions that help to bridge the gap between the textbook and the clinical arena.

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Taylor RB, David AK, Fields SA, Phillips DM, Scherger JE. *Family Medicine, Principle and Practice*. 7th ed. New York, NY: Springer-Verlag; 2007

SECTION II

Clinical Cases

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Case 1

A 52-year-old man comes to your office for a routine physical examination. He is a new patient to your practice. He has no significant medical history and takes no medications regularly. His father died at the age of 74 of a heart attack. His mother is alive at the age of 80. She has hypertension. He has two younger siblings with no known chronic medical conditions. He does not smoke cigarettes, drink alcohol, use any recreational drugs, and does not exercise. On examination, his blood pressure is 127/82 mm Hg, pulse is 80 beats/min, respiratory rate is 18 breaths/min, height is 67 in, and weight is 190 lb. On careful physical examination, no abnormalities are noted.

- What screening test(s) for cardiovascular disease should be recommended for this patient?
- What screening test(s) for cancer should be recommended?
- What immunization(s) should be recommended?

ANSWERS TO CASE 1:
Adult Male Health Maintenance

Summary: A 52-year-old man with no active medical problems is being evaluated during an "annual physical." He has no complaints on history and has a normal physical examination.

- **Recommended screening tests for cardiovascular conditions:** Blood pressure measurement (screening for hypertension) and lipid measurement (screening for dyslipidemia)
- **Recommended screening tests for cancer:** Fecal occult blood testing, flexible sigmoidoscopy (with or without occult blood testing), colonoscopy or double-contrast barium enema to screen for colorectal cancer; there is insufficient evidence to recommend for or against universal prostate cancer screening by prostate-specific antigen (PSA) testing
- **Recommended immunizations:** Tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) if he has not had one before and if it has been 10 years or more since he has had a Tetanus-diphtheria (Td) vaccine or if he requires booster protection against pertussis; influenza vaccine annually, in the fall or winter months

ANALYSIS

Objectives

1. Know the components of an adult health-maintenance visit.
2. Learn the screening tests and immunizations that are routinely recommended for adult men.

Considerations

The patient described is a healthy 52-year-old man. Health maintenance should be employed to prevent future disease. In general, the approach is immunizations, cancer screening, and screening for common diseases. Generally colon cancer screening should be initiated at age 50 and beyond. The influenza vaccine should be recommended annually, and the tetanus vaccine every 10 years. The acellular pertussis vaccine is also recommended as many adults have had waning immunity to pertussis and occasional outbreaks of whooping cough have been noted. Since cardiovascular disease is the most common cause of mortality in his age group, screening for cardiovascular disease or risk factors is appropriate.

APPROACH TO
Health Maintenance

DEFINITIONS

SCREENING TEST: Assessment device or test that should be cost effective with high sensitivity and can be used on a large population.

HEALTH MAINTENANCE: Preventative care for patients prior to development of disease.

CLINICAL APPROACH

For years, one of the cornerstones of primary care was the "annual physical," which often consisted of a complete physical examination, blood tests, including complete blood counts (CBCs) and multichemistry panels, and, frequently, annual chest x-rays and electrocardiograms (ECGs). The concept of the "annual physical," or "health-maintenance examination" is still important; however, the components of the examination have changed over time.

The purposes of the health-maintenance visit are to identify the individual patient's health concerns, manage the patient's current medical conditions, identify the patient's risks for future health problems, perform rational and cost-effective health screening tests, and promote a healthy lifestyle. Prevention is divided into primary prevention and secondary prevention. **Primary prevention** is an intervention designed to prevent a disease before it occurs. It usually involves the identification and management of risk factors for a disease. Examples of this would be the use of a statin medication to reduce low-density lipoprotein (LDL) cholesterol in order to lower the risk of coronary artery disease or the removal of colon polyps to prevent the development of colon cancer. **Secondary prevention** is an intervention intended to reduce the recurrence or exacerbation of a disease. An example of secondary prevention is the use of a statin medication after a person has had a myocardial infarction (MI) so as to reduce the risk of a second heart attack.

Effective screening for diseases or health conditions should meet several established criteria. First, the disease should be of **high enough prevalence** in the population to make the screening effort worthwhile. There should be a time frame during which the person is asymptomatic, but during which the disease or risk factor can be identified. There needs to be a test available for the disease that has **sufficient sensitivity and specificity, is cost-effective,** and is **acceptable** to patients. Finally, there must be an intervention that can be made during the asymptomatic period that will prevent the development of the disease or reduce the morbidity/mortality of the disease process.

The United States Preventive Services Task Force (USPSTF) is an independent panel of experts in primary care and preventive medicine that reviews evidence and makes recommendations on the effectiveness of clinical preventive services, specifically in the areas of screening, immunization, preventive medications, and counseling. USPSTF recommendations are "gold standards" for clinical preventive medicine. The recommendations of the USPSTF are available online for free at www.preventiveservices.ahrq.gov. USPSTF grades its recommendations in five categories:

A: There is strong evidence that the intervention improves health outcomes and its benefits substantially outweigh its potential harms. These services are strongly recommended.
B: There is at least fair evidence that the intervention improves health outcomes and its benefits outweigh its potential harms. These services are recommended.
C: The balance of the benefits and potential harms is too close to justify making a general recommendation.
D: There is at least fair evidence that the service is ineffective or the potential harms outweigh the benefits. These services are not recommended.
E: There is insufficient evidence, or the available evidence is of such poor quality, that the balance of benefits and harms cannot be weighed and recommendations for or against the service cannot be made.

SCREENING TESTS

Cardiovascular Diseases

Diseases of the cardiovascular system are the leading cause of death in adult men and the management of risk factors for these diseases reduces both morbidity and mortality from these diseases. The USPSTF strongly recommends (Level A) screening of adults for **hypertension** by measurement of blood pressure, as screening causes little harm and management of hypertension is effective at reducing the risk of cardiovascular diseases. USPSTF also strongly recommends (Level A) screening men aged 35 years or more and women aged 45 years or more for **lipid disorders** and recommends (Level B) screening adults older than 20 years who are at increased risk for cardiovascular diseases. The screening can take the form of nonfasting total cholesterol and high-density lipoprotein (HDL)-cholesterol levels or fasting lipid panels that include the low-density lipoprotein (LDL)-cholesterol. Ultrasonography to assess for **abdominal aortic aneurysm** is recommended (Level B) for men aged 65 to 75 years who have ever smoked. There is no recommendation (Level C) for abdominal aortic aneurysm screening for men who have never smoked and it is recommended against (Level D) for women, regardless of smoking status.

The routine use of electrocardiogram (ECG), exercise stress testing, or computed tomography (CT) scanning for coronary calcium is not recommended (Level D) for screening for **coronary artery disease** in adults at low risk for coronary events. There is insufficient evidence to recommend for or against these modalities (Level I) in adults at higher risk of coronary events. Screening for **peripheral arterial disease** in asymptomatic adults is not recommended (Level D) because of the low prevalence of the problem in asymptomatic adults and the lack of evidence for improved outcomes from treatment in the asymptomatic stage.

Cancer

Adults (men and women) older than 50 years are strongly advised (Level A) to have screening for **colorectal cancer.** This screening can take the form of fecal occult blood testing (FOBT) using guaiac cards on three consecutive bowel movements collected at home, flexible sigmoidoscopy with or without occult blood testing, double-contrast barium enema, or colonoscopy. The optimal intervals for testing are not clear, but FOBT is generally recommended annually, sigmoidoscopy and barium enema every 3 to 5 years, and colonoscopy every 10 years. An abnormal test result of FOBT, sigmoidoscopy, or barium enema leads to the performance of a colonoscopy.

The USPSTF currently finds insufficient evidence to recommend for or against routine screening (Level I) for **prostate cancer** using digital examination or prostate-specific antigen (PSA) in men younger than 75 years. Although testing improves detection of prostate cancer, the evidence for improved outcomes is inconsistent. Level I ratings are also given to screening for **lung cancer** using CT scanning, chest x-rays, sputum cytology, or combinations of these, and to screening for skin cancer or oral cancer.

Screening for **bladder, testicular, pancreatic, or thyroid cancer** in asymptomatic adults is not recommended (Level D). Screening for prostate cancer in asymptomatic men older than 75 years is also not recommended (Level D).

Other Health Conditions

Screening for **obesity** by measuring body mass index (BMI) and providing intensive counseling and behavioral interventions to promote weight loss are recommended for all adults (Level B). There is insufficient evidence to recommend screening of asymptomatic adults for **type II diabetes mellitus** (Level I), although screening is recommended (Level B) for adults with hypertension or hyperlipidemia. **Depression** screening is recommended (Level B) if there are mechanisms in place for assuring accurate diagnosis, treatment, and follow-up. Screening and counseling to identify and promote cessation of **tobacco use** is strongly recommended (Level A). Screening and counseling to identify and prevent the **misuse of alcohol** is also recommended (Level B).

IMMUNIZATIONS

As is the case for well-child care, the provision of age- and condition-appropriate immunizations is an important component of well-adult care. Recommendations for immunizations change from time to time and the most up-to-date source of vaccine recommendations is the Advisory Committee on Immunization Practices. Its immunization schedules are widely published and are available at the Centers for Disease Control and Prevention Web site (among other places), www.cdc.gov.

The CDC has recently recommended that all adults between 19 and 65 years of age should receive a booster of Tdap in place of a scheduled dose of Td due to waning immunity against pertussis and the presence of an increasing number of cases of pertussis nationwide. Adults who have not had a Td booster in 10 years or more and who have never had a dose of Tdap should receive a booster vaccination with Tdap. Persons who may need an increase in protection against pertussis, including health-care workers, childcare providers, or those who anticipate having close contact with infants younger than 1 year, should also receive a Tdap booster. An interval of 2 years from the last Td is recommended, although a shorter interval may be used if necessary.

Influenza vaccination is recommended every year for adults older than 50 years. It is also recommended annually for those younger than 50 years with certain medical conditions and for persons who may transmit the infection to others who are at high risk (health-care or nursing home workers, household contacts of high-risk individuals, etc). High-risk conditions include chronic diseases of the cardiovascular, pulmonary, and renal systems and metabolic diseases such as diabetes, hemoglobinopathies, and immunodeficiencies.

Pneumococcal polysaccharide vaccination is recommended as a single dose for all adults aged 65 years or older. It is also recommended for adults younger than 65 years who have chronic cardiovascular, pulmonary, renal, or hepatic diseases, diabetes, or an immunodeficiency, or who are functionally asplenic. One-time revaccination after 5 years is recommended for those with chronic kidney or hepatic disease, immunodeficiency, or asplenia. One-time revaccination is also recommended for those older than 65 years if they were vaccinated longer than 5 years previously and were younger than 65 years at the time of initial vaccination.

Other vaccinations may be recommended for specific populations, although not for all adults. **Hepatitis B** vaccination should be recommended for those at high risk of exposure, including health-care workers, those exposed to blood or blood products, dialysis patients, intravenous drug users, persons with multiple sexual partners or recent sexually transmitted diseases, and men who engage in sexual relations with other men. **Hepatitis A** vaccine is recommended for persons with chronic liver disease, who use clotting factors, who have occupational exposure to the hepatitis A virus, who use IV drugs, men who have sex with men, or who travel to countries where hepatitis A

is endemic. **Varicella** vaccination is recommended for those with no reliable history of immunization or disease, who are seronegative on testing for varicella immunity, and who are at risk for exposure to varicella virus. **Meningococcal** vaccine is recommended for persons with certain complement deficiencies, functional or anatomic asplenia, or who travel to countries where the disease is endemic.

HEALTHY LIFESTYLE

Along with the discussion of screening and promotion of tobacco cessation and prevention of alcohol misuse, other aspects of healthy living should be promoted by physicians. **Exercise** has been consistently shown to reduce the risk of cardiovascular disease, diabetes, obesity, and overall mortality. Even exercise of moderate amounts, such as walking for 30 minutes on most days of the week, has a positive effect on health. The benefits increase with increasing the amount of exercise performed. Studies performed on counseling physically inactive persons to exercise have shown inconsistent results. However, the benefits of exercise are clear and should be promoted. Counseling to promote a healthy **diet** in persons with hyperlipidemia, other risk factors for cardiovascular disease, or other conditions related to diet is beneficial. Intensive counseling by physicians or, when appropriate, referral to dietary counselors or nutritionists, can improve health outcomes. In selected patients, recommendations regarding **safer sexual practices,** including the use of condoms, may be appropriate to reduce the risk or recurrence of sexually transmitted diseases. Finally, all patients should be encouraged to use **seat belts** and avoid driving while under the influence of alcohol or drugs, as motor vehicle accidents remain a leading cause of morbidity and mortality in adults.

Comprehension Questions

1.1 A 52-year-old man comes into the outpatient clinic for an annual "checkup." He is in good health, and has a relatively unremarkable family history. For which of the following disorders should a screening test be performed?

A. Prostate cancer
B. Lung cancer
C. Abdominal aortic aneurysm
D. Colon cancer

1.2 A 62-year-old man with recently diagnosed emphysema presents to your office in November for a routine examination. He has not had any immunizations in more than 10 years. Which of the following immunizations would be the most appropriate for this individual?

A. Tetanus-diphtheria (Td) only
B. Tdap, pneumococcal, and influenza
C. Pneumococcal and influenza
D. Tdap, pneumococcal, influenza, and meningococcal

1.3 A 49-year-old sedentary man has made an appointment because his best friend died of an MI at age 50. He asks about an exercise and weight loss program. In counseling him, which of the following statements regarding exercise is most accurate?

A. To be beneficial, exercise must be performed everyday.
B. Walking for exercise has not been shown to improve meaningful clinical outcomes.
C. Counseling patients to exercise has not been shown consistently to increase the number of patients who exercise.
D. Intense exercise offers no health benefit over mild to moderate amounts of exercise.

ANSWERS

1.1 **D.** Colon cancer screening is given a Level A recommendation by the USPSTF and is routinely recommended for all adults older than 50 years. There is insufficient evidence to recommend for or against routine lung or prostate cancer screening. Abdominal aortic aneurysm screening is recommended in men aged 65 to 75 years who have smoked.

1.2 **B.** In an adult with a chronic lung disease, one-time vaccination with pneumococcal vaccine and annual vaccination with influenza vaccine are recommended. A Tdap booster should be recommended to all adults who have not had a Td booster within 10 years and have never had a Tdap vaccine.

1.3 **C.** The benefits of exercise are clear. Exercise decreases cardiovascular risk factors, increases insulin sensitivity, decreases the incidence of the metabolic syndrome, and decreases cardiovascular mortality regardless of obesity. The benefits of counseling patients regarding exercise are not so clear and counseling does not seem to increase the number of patients who exercise.

Clinical Pearls

- There is no such thing as "routine blood tests" or a "routine chest x-ray." All tests that are ordered should have evidence to support their benefit.
- High-quality, evidence-based recommendations for preventive health services are available at www.preventiveservices.ahrq.gov.

REFERENCES

Blaha, MJ et al. "A Practical "ABCDE" Approach to the Metabolic Syndrome." *Mayo Clinic Proceedings*. August 2008;83(8): 932-943.

Centers for Disease Control and Prevention Web site: http://www.cdc.gov.

United States Preventive Services Task Force Web site: http://www.preventiveservices.ahrq.gov.

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Case 2

A 52-year-old man presents to your office for an acute visit because of coughing and shortness of breath. He is well known to you because of multiple office visits in the past few years for similar reasons. He has a chronic "smoker's cough," but reports that in the past 2 days his cough has increased, his sputum has changed from white to green in color, and he has had to increase the frequency with which he uses his albuterol inhaler. He denies having a fever, chest pain, peripheral edema, or other symptoms. His medical history is significant for hypertension, peripheral vascular disease, and two hospitalizations for pneumonia in the past 5 years. He has a 60-pack-year history of smoking and continues to smoke two packs of cigarettes a day.

On examination, he is in moderate respiratory distress. His temperature is 98.4°F, his blood pressure is 152/95 mm Hg, his pulse is 98 beats/min, his respiratory rate is 24 breaths/min, and he has an oxygen saturation of 94% on room air. His lung examination is significant for diffuse expiratory wheezing and a prolonged expiratory phase of respiration. There are no signs of cyanosis. The remainder of his examination is normal. A chest x-ray done in your office shows an increased anteroposterior (AP) diameter and flattened diaphragms, but otherwise he has clear lung fields.

- What is the most likely cause of this patient's dyspnea?
- What acute treatment(s) are most appropriate at this time?
- What interventions would be most helpful to reduce the risk of future exacerbations of this condition?

ANSWERS TO CASE 2:
Dyspnea (Chronic Obstructive Pulmonary Disease)

Summary: A 52-year-old man with a long smoking history presents with dyspnea, increased sputum production, coughing, and wheezing.

- **Most likely cause of current symptoms:** Acute exacerbation of chronic obstructive pulmonary disease (COPD)
- **Appropriate treatment of exacerbation:** Antibiotic, bronchodilators, systemic corticosteroids
- **Interventions to reduce exacerbations:** Smoking cessation, long-acting bronchodilator, inhaled corticosteroid, influenza vaccination

ANALYSIS

Objectives

1. Be able to diagnose and determine the stage of COPD in adults.
2. Know the management of stable COPD and COPD exacerbations.

Considerations

Two of the most common causes of dyspnea and wheezing in adults are asthma and COPD. There can be substantial overlap between the two diseases, as patients with chronic asthma can develop chronic obstructive disease over time. As in most medical situations, the patient's history will usually provide the key information to the appropriate diagnosis. Asthma often presents earlier in life, may or may not be associated with cigarette smoking, and is characterized by episodic exacerbations with return to relatively normal baseline lung functioning. COPD, on the other hand, tends to present in midlife or later, is usually the result of a long-term history of smoking, and is a slowly progressive disorder in which measured pulmonary functioning never returns to normal.

In the setting of an acute exacerbation, the differentiation between an exacerbation of asthma and an exacerbation of COPD is not necessary for determination of the immediate management. The assessment of the patient presenting with dyspnea should always start with the ABCs—**A**irway, **B**reathing, and **C**irculation. Intubation with mechanical ventilation should be performed when the patient is unable to protect his own airway (for example, when he has a reduced level of consciousness), when he is tiring because of the amount

of work required to overcome his airway obstruction, or when adequate oxygenation cannot be maintained.

For both asthma and COPD exacerbations, the mainstays of medical therapy are oxygen, bronchodilators, and steroids. All dyspneic patients should have an assessment of their level of oxygenation. Clinical signs of hypoxemia, such as cyanosis of the perioral region or digits, should be noted on examination. Objective levels of oxygenation using pulse oximetry or arterial blood gas measurements should also be performed. Hypoxemia must be addressed by providing supplemental oxygen. Inhaled β_2-agonists, most commonly albuterol, can rapidly result in bronchodilation and reduction in airway obstruction. The addition of an inhaled anticholinergic agent, such as ipratropium, may work synergistically with the β-agonist. Corticosteroids, given systemically (orally, intramuscularly, or intravenously), act to reduce the airway inflammation that underlies the acute exacerbation. Clinically significant effects of steroids take hours to occur; consequently, steroids should be used with bronchodilators because bronchodilators act rapidly. Steroids used in combination with bronchodilators significantly improve short-term outcomes in the management of acute exacerbations of asthma and COPD.

APPROACH TO
Chronic Obstructive Pulmonary Disease

DEFINITIONS

CHRONIC BRONCHITIS: Cough and sputum production on most days for at least 3 months during at least two consecutive years.

EMPHYSEMA: Shortness of breath caused by the enlargement of respiratory bronchioles and alveoli caused by destruction of lung tissue.

CLINICAL APPROACH

Evaluation

COPD is defined as airway obstruction that is not fully reversible, is usually progressive, and is associated with chronic bronchitis, emphysema, or both. The most common etiology is **cigarette smoking,** which is **associated with approximately 90% of cases of COPD.** Other etiologies of COPD include passive exposure to cigarette smoke ("second-hand smoke") and occupational exposures to dusts or chemicals. A rare cause of COPD is a genetic deficiency in **α_1-antitrypsin,** which is more common in Caucasians and should be considered when emphysema develops at younger ages (<45 years of age), especially

in nonsmokers. COPD is a disease of inflammation of the airways, lung tissue, and vasculature. Pathologic changes include mucous gland hypertrophy with hypersecretion, ciliary dysfunction, destruction of lung parenchyma, and airway remodeling. The results of these changes are narrowing of the airways, causing a fixed airway obstruction, poor mucous clearance, cough, wheezing, and dyspnea.

The most common initial symptom of COPD is cough, which is at first intermittent and then frequently becomes a daily occurrence. The cough is often productive of white, thick mucus. Patients will present with intermittent episodes of worsening cough, with change in mucus from clear to yellow/green, and often with wheezing. These exacerbations are usually caused by viral or bacterial infections.

As COPD progresses, lung function continues to deteriorate and dyspnea develops. Dyspnea is the primary presenting symptom of COPD. Dyspnea also tends to worsen over time—initially the dyspnea will occur only with significant effort, then with any exertion, and finally at rest. **By the time dyspnea develops, lung function (as measured by forced expiratory volume in the first second of expiration [FEV_1]) has been reduced by about half and the COPD has been present for years.**

Examination of a patient with mild or moderate COPD, who is not having an exacerbation, is usually normal. As the disease progresses, patients are often noted to have "barrel chests" (increased anteroposterior chest diameter) and distant heart sounds, as a result of hyperinflation of the lungs. Breath sounds may also be distant and expiratory wheezes with a prolonged expiratory phase of respiration may be noted. During an acute exacerbation, patients often appear anxious and tachypneic; they may be using accessory muscles of respiration, usually have wheezes or rales, and may have signs of cyanosis.

Chest x-rays in patients with COPD are typically normal until the disease is advanced. In more severe cases, hyperinflation of the lungs with an increased posteroanterior (PA) diameter and flattening of diaphragms may be seen. Bullae—areas of pulmonary parenchymal destruction—can also be seen in x-rays in more severe disease.

The primary diagnostic test of lung function is spirometry. In normal aging, both the forced vital capacity (FVC) (a measure of the total amount of air that can be expired after a maximal inspiration) and forced expiratory volume in first second (FEV_1) reduce gradually over time. In normal-functioning lungs, the ratio of the FEV_1 to FVC is greater than 0.7. **In COPD, both the FVC and FEV_1 are reduced and the ratio of FEV_1 to FVC is less than 0.7,** indicating an airway obstruction. **Reversibility is defined as an increase in FEV_1 of greater than 12% or 200 mL.** Using a bronchodilator may result in some improvement of both FVC and FEV_1, but neither will return to normal, making the diagnosis of a fixed obstruction. The severity of COPD, which can help to determine treatment, can be assessed using these measurements (Table 2–1).

Table 2–1 CLASSIFICATION OF COPD SEVERITY

STAGE	CLASSIFICATION	FINDINGS	TREATMENT
0	At risk	Cough, sputum production Normal spirometry	Vaccines and smoke cessation
I	Mild COPD	$FEV_1/FVC < 0.7$ $FEV_1 \geq 80\%$ predicted With or without symptoms	Short-acting bronchodilators
II	Moderate COPD	$FEV_1/FVC < 0.7$ FEV_1 50%-80% predicted With or without symptoms	Long-acting bronchodilators
III	Severe COPD	$FEV_1/FVC < 0.7$ FEV_1 30%-50% predicted With or without symptoms	Inhaled steroids
IV	Very severe COPD	$FEV_1/FVC < 0.7$ FEV_1 <30% predicted or FEV_1 <50% predicted with chronic hypoxemia	Consider oxygen therapy

Adapted from NHLBI/WHO. Global initiative for chronic obstructive lung disease, executive summary, 2005.

Management of Stable COPD

The goals of COPD management are to relieve symptoms, slow disease progression, reduce/prevent/treat exacerbations, and reduce/prevent/treat complications. Several components of treatment are common to all stages of COPD, whereas pharmacologic treatment is guided by the stage of disease.

All patients with COPD should be encouraged to quit smoking. The pulmonary function of smokers declines more rapidly than that of nonsmokers. **Although smoking cessation does not result in significant improvement in pulmonary function, smoking cessation does reduce the rate of further deterioration to that of a nonsmoker.** Cessation also reduces the risks of other comorbidities, including cardiovascular diseases and cancers. Case 7 more thoroughly discusses smoking cessation. All patients with COPD should receive a pneumococcal and annual influenza vaccination. Influenza vaccination reduces the frequency and complications of exacerbations. Regular exercise and efforts to maintain normal body weight should be encouraged.

Short-acting bronchodilators used as needed are the recommended treatment in stage I COPD. These include β_2-agonists (albuterol) and anticholinergics (ipratropium). **Inhaled medications are preferred over oral,** as they

tend to have fewer side effects. The choice of specific agent is based on availability, individual response to therapy, and side effects.

In stage II COPD, a long-acting bronchodilator should be added. Commonly used agents in the United States are salmeterol (an inhaled β_2-agonist) and tiotropium (an inhaled anticholinergic). Oral methylxanthines (aminophylline, theophylline) are also options, but have narrow therapeutic windows (high toxicity) and multiple drug-drug interactions, making their use less common. The use of long-acting bronchodilators is more convenient and more effective than using short-acting agents, but is much more expensive and does not replace the need for short-acting agents for rescue therapy in exacerbations.

Inhaled steroids (fluticasone, triamcinolone, mometasone, etc) do not affect the rate of decline of lung function in COPD but do reduce the frequency of exacerbations. For that reason, **inhaled steroids are recommended for stages III and IV COPD with frequent exacerbations.** Long-term treatment with oral steroids is not recommended, as there is no evidence of benefit, but there can be multiple complications (myopathy, osteoporosis, glucose intolerance, etc).

Oxygen therapy is recommended in stage IV COPD if there is evidence of hypoxemia ($PaO_2 \leq 55$ mm Hg or $SaO_2 \leq 88\%$ at rest) or where the PaO_2 is less than or equal to 60 mm Hg and there is polycythemia, pulmonary hypertension, or peripheral edema suggesting heart failure. **Oxygen therapy is the only intervention that has been shown to decrease mortality and must be worn for at least 15 h/d.**

Management of Exacerbations of COPD

Acute exacerbations of COPD are common and typically present with change in sputum color or amount, cough, wheezing, and increased dyspnea. Viral and bacterial infections are a common precipitant of acute exacerbations of COPD. Diagnoses that can cause similar symptoms (eg, pulmonary embolism, congestive heart failure, myocardial infarction) must be excluded so that appropriate therapy can occur.

The severity of the exacerbation should be evaluated by history, examination, assessment of oxygenation, and focused testing. Oxygen should be given to keep saturation greater than 90% or PaO_2 levels at about 60 mm Hg. Patients with more severe symptoms, comorbidities, altered mental status, an inability to care for themselves at home, or whose symptoms fail to respond promptly to office or emergency room treatments should be hospitalized.

All acute exacerbations should be treated with short-acting bronchodilators. Combinations of short-acting agents with different mechanisms of action (ie, β-agonist and anticholinergic) can be used until symptoms improve. **Systemic steroids shorten the course of the exacerbation and may reduce the risk of relapse.** A steroid dose of 40 mg prednisone (or equivalent) for 10 to 14 days is recommended.

Exacerbations associated with increased amounts of sputum or with purulent sputum should be treated with antibiotics. *Pneumococcus, Haemophilus influenzae, and Moraxella catarrhalis* are the most common bacteria implicated. In milder exacerbations, treatment with oral agents directed against these pathogens is appropriate. In severe exacerbations, gram-negative bacteria (*Klebsiella, Pseudomonas*) can also play a role, so antibiotic coverage needs to be broader.

Comprehension Questions

2.1 A 38-year-old woman presents with progressively worsening dyspnea and cough. She has never smoked cigarettes, has no known passive smoke exposure, and does not have any occupational exposure to chemicals. Pulmonary function testing shows obstructive lung disease that does not respond to bronchodilators. Which of the following is the most likely etiology?

A. Radon exposure at home
B. COPD
C. α_1-Antitrypsin deficiency
D. Asthma

2.2 A 60-year-old man is diagnosed with moderately severe (stage II) COPD. He admits to a long history of cigarette smoking and is still currently smoking. In counseling him about the benefits of smoking cessation, which of the following statements is most accurate?

A. By quitting, his pulmonary function will significantly improve.
B. By quitting, his current pulmonary function will be unchanged, but the rate of pulmonary function decline will slow.
C. By quitting, his pulmonary function currently and rate of decline are unchanged, but there are cardiovascular benefits.
D. By quitting, his pulmonary function will approach that of a nonsmoker of the same age.

2.3 A 68-year-old patient of your practice with known COPD has pulmonary function testing showing an FEV_1 of 40% predicted has been having frequent exacerbations of his COPD. His SaO_2 by pulse oximetry is 91%. Which of the following medication regimens is the most appropriate?

A. Inhaled salmeterol BID and albuterol as needed
B. Oral albuterol daily and inhaled fluticasone BID
C. Inhaled fluticasone BID, inhaled tiotropium BID, and inhaled albuterol as needed
D. Inhaled fluticasone BID, inhaled tiotropium BID, inhaled albuterol as needed, and home oxygen therapy

2.4 A 59-year-old man with a known history of COPD presents with worsening dyspnea. On examination he is afebrile. His breath sounds are decreased bilaterally. He is noted to have jugular venous distension (JVD) and 2+ pitting edema of the lower extremities. Which of the following is the most likely cause of his increasing dyspnea?

A. COPD exacerbation
B. Pneumonia
C. cor pulmonale
D. Pneumothorax

ANSWERS

2.1 **C.** This patient has a fixed airway obstruction consistent with COPD. The airway obstruction of asthma would be at least partially reversible on testing with a bronchodilator. α_1-Antitrypsin deficiency should be considered in a patient who develops COPD at a young age, especially if there is no other identifiable risk factor.

2.2 **B.** Smoking cessation will not result in reversal of the lung damage that has already occurred, but can result in a slowing in the rate of decline of pulmonary function. In fact, smoking cessation can result in the rate of decline returning to that of a nonsmoker.

2.3 **C.** This patient has stage III COPD with frequent exacerbations. He is best treated by a long-acting bronchodilator (eg, tiotropium) and an inhaled steroid (eg, fluticasone) used regularly, along with an inhaled, short-acting bronchodilator on an as-needed basis.

2.4 **C.** JVD and lower extremity edema are suggestive of cor pulmonale, which is right heart failure due to chronically elevated pressures in the pulmonary circulation. Right heart failure causes increased right atrial pressures and right ventricular end diastolic pressures, which then lead to liver congestion, jugular venous distension, and lower extremity edema.

Clinical Pearls

- All smokers should be counseled on the benefits of smoking cessation before they develop symptomatic COPD; by the time symptoms develop, the patient's FEV_1 will have reduced by approximately 50%.
- Always remember to evaluate the ABCs—**A**irway, **B**reathing, **C**irculation—when evaluating a dyspneic patient.

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Case 3

A 45-year-old white man presents to your office complaining of left knee pain that started last night. He says that the pain started suddenly after dinner and was severe within a span of 3 hours. He denies any trauma, fever, systemic symptoms, or prior similar episodes. He has a history of hypertension for which he takes hydrochlorothiazide (HCTZ). He admits to consuming a great amount of wine last night with dinner.

On examination, his temperature is 98°F, his pulse is 90 beats/min, his respirations are 22 breaths/min, and his blood pressure is 129/88 mm Hg. Heart and lung examinations are unremarkable. The patient is reluctant to flex the left knee, wincing in pain at touch, and has passive range of motion. The knee is edematous, hot to touch, and has erythema of the overlying skin. No crepitation or deformity is apparent. No other joints are involved. Inguinal lymph nodes are not enlarged. Complete blood count reveals a white blood cell count of 10,900 cells/mm^3 and is otherwise normal.

- What is the next diagnostic step?
- What is the most likely diagnosis?
- What is the next step in therapy?

ANSWERS TO CASE 3:
Joint Pain

Summary: This is a 45-year-old man who presents with the sudden onset of monoarticular, nontraumatic joint pain. Evolution from onset to severe pain was rapid. The patient denies any trauma, systemic signs of illness, or any prior episodes. That he takes hydrochlorothiazide and drank a lot of alcohol the night that his symptoms started are important. His vital signs are stable, and he does not appear to be systemically ill. There is pain to movement and touch of the left knee, with evident edema, erythema, and warmth of the joint. No other joints are involved. His white blood cell count is not indicative of an acute infectious process.

- **Next diagnostic step:** Joint aspiration for examination of joint fluid to identify crystals and exclude infection
- **Most likely diagnosis:** Crystal-induced gout of the left knee
- **Next step in therapy:** Nonsteroidal anti-inflammatory drug (NSAID) and provide analgesia; may consider using colchicine

ANALYSIS

Objectives

1. Have a differential diagnosis for nontraumatic joint pain, based on clinical presentation.
2. Be familiar with the most common diagnostic tests for the above conditions, and have a rationale when ordering these tests.
3. Know the most common treatment options in the acute onset of gout and infectious arthritis, as well as the chronic management of rheumatoid arthritis and osteoarthritis.

Considerations

This 45-year-old man presents with the sudden onset of monoarticular joint pain. **The first diagnosis that needs to be excluded is an infected joint.** A joint becomes septic by blood inoculation, by contiguous infection (such as from bone or soft tissue), or from direct inoculation from trauma or surgery. Exclusion of an infectious etiology is paramount as cartilage can be destroyed within the first 24 hours of infection. In this case, the patient's history and clinical scenario do not favor an infectious cause, although it cannot be excluded by history and physical examination alone.

There are several additional pieces of information that guide the diagnosis in this case. Most gout attacks occur between the ages of 30 and 50 years in men, with a later onset in postmenopausal women (50 to 70 years of age). The patient's recent increase in alcohol consumption can be considered an exacerbating factor. Other factors that may also increase the risk of a gout attack include trauma, surgery, or a large meal that induces hyperuricemia. Finally, the patient's history of taking a **thiazide diuretic** is also important, as these drugs **may induce hyperuricemia.**

The examination of a joint aspirate is essential for the diagnosis. The **gross appearance of fluid is not very specific,** as both a septic aspirate and a heavily condensed crystal-induced arthritis may have a thick, yellowish/chalky appearance. To diagnose crystal-induced arthritis, polarizing microscopy has to reveal monosodium urate (MSU) crystals, which will look like needles and have a strong negative birefringence. Other crystals that may be seen are **calcium pyrophosphate dehydrate, calcium hydroxyapatite, and calcium oxalate**.

- **Calcium pyrophosphate dehydrate**: Rod shaped, rhomboid, weakly positive birefringence
- **Calcium hydroxyapatite**: Seen by electron microscopy, cytoplasmic inclusions that are nonbirefringent
- **Calcium oxalate**: Bipyramidal appearance, strongly positive birefringence; seen mostly in end-stage renal disease patients

In crystal-induced arthritis, the white blood cell count of the joint aspirate is on average 2000 to 60,000/μL, with less than 90% neutrophils, while a septic joint will have an average of 100,000 WBC/μL (25,000-250,000 cells) with more than 90% neutrophils. Aspirate that has been determined to be crystal-induced must also be cultured so as to rule out a coexisting infection.

APPROACH TO
Nontraumatic Joint Pain/Swelling

DEFINITIONS

GOUTY ARTHRITIS: Condition of excess uric acid leading to deposition in joints, especially the great toe.

PSEUDOGOUT: Condition of joint pain and inflammation due to **calcium pyrophosphate dehydrate crystals in the joints, which can be diagnosed by noting** rod-shaped, rhomboid, weakly positive birefringence by crystal analysis.

CLINICAL APPROACH

Depending on the etiology, pain may be present in 1, 2, or more joints. Considering the patient's age, medical history, and medication profile is important. The patient's lifestyle and social history should also be considered, as certain activities may predispose a patient to specific infections. Among **the major diagnoses that have to be considered in a nontraumatic swollen joint are gout (or any crystal-induced arthritis), infectious arthritis, osteoarthritis, and rheumatoid arthritis.** For acute monoarticular arthritis in adults, the most common causes include trauma, crystals, and infection.

Clinical Presentation

Gout's first episode can often be confused with cellulitis. It presents with swelling and pain, usually of one joint, accompanied by erythema and warmth. **Classically, a gout attack involves the metatarsophalangeal joint of the first toe,** called **podagra,** but it may involve any joint in the body. Some cases left untreated resolve spontaneously within 3 to 10 days, with no residual signs or symptoms. **During an acute attack, the serum uric acid level may be normal or even low,** likely as a result of the existing deposition of the urate crystals. Uric acid levels are, however, useful in monitoring hypouricemic therapy between attacks. Radiographs may show cystic changes in the joint surface, with punched-out lesions and soft-tissue calcifications. These findings are nonspecific and are also seen in osteoarthritis and rheumatoid arthritis.

An infection usually involves only one joint if it is of bacterial origin (>90% of cases). The knee, hip, and shoulder are the three most commonly involved joints. A *chronic* monoarticular arthritis or involvement of two to three joints may be caused by fungi or mycobacteria. In the case of acute polyarticular (>3 joints) arthritis, the etiology may be from endocarditis or a disseminated gonococcal infection.

Bacterial infections of a joint occur most commonly in persons with rheumatoid arthritis. The chronic inflammation of joints coupled with the use of steroids predisposes this group to *Staphylococcus aureus* infections. HIV-positive patients may develop pneumococcal, salmonella, or even *Haemophilus influenzae* joint infections. Intravenous drug users are most likely to get a streptococcal, staphylococcal, gram-negative, or *Pseudomonas* infection.

Range of motion (ROM) of the joint is an important maneuver of the physical examination. **A septic joint will have a very limited ROM due to pain** coupled with a joint effusion and fever. However, a nearby cellulitis, bursitis, or osteomyelitis will usually maintain the ROM of a joint. The aspirate of a septic joint will have a positive culture in more than 90% of cases.

Osteoarthritis (OA) is most commonly found in people older than 65 years of age (68% of patients) and is associated with trauma, history of repetitive joint use, and obesity (specifically for knee OA). It primarily affects the cartilage, but ends up damaging the bone surface, synovium, meniscus, and ligaments. The

clinical presentation is usually that of a dull, deep, ache-type pain. The onset is usually gradual, with activity exacerbating the pain, and rest decreasing it. In the latter stages, pain is usually constant. On physical examination, a bony crepitus may be felt on passive ROM. There may be a small joint effusion and periarticular muscle atrophy. In the advanced stage, joint deformity with decreased ROM will be seen. **X-rays are usually normal at first,** with the gradual development of bone sclerosis, subchondral cysts, and osteophytes.

Rheumatoid arthritis (RA) is another common disorder that may affect people from any age group, but will usually present initially in those 30 to 55 years old. The presentation of RA can be varied, ranging from a monoarticular arthritis that is intermittent, to a polyarthritis that progresses gradually in intensity, leading to disability. It affects more women than men (3:1), and the treatment will usually depend on the stage at which the disease is diagnosed. The American Rheumatism Association has delineated **specific diagnostic criteria to aid in the diagnosis of RA,** among which are the following:

1. Morning stiffness
2. Involvement of three or more joints
3. Involvement of hand joints
4. Symmetric arthritis
5. Presence of rheumatoid nodules
6. Positive rheumatoid factor
7. Radiographic changes, which include erosions or decalcifications.

Of all these diagnostic criteria, the **first four must be present for at least 6 weeks,** and the **fulfillment of any four of these criteria is sufficient to diagnose RA.** Among the laboratory tests that may be abnormal in patients with RA are an elevated erythrocyte sedimentation rate, an elevated C-reactive protein, anemia, thrombocytosis, and low albumin. The level of hypoalbuminemia usually correlates with the severity of the disease.

Treatment

Analgesia is a common factor to consider in therapy for all the conditions described above. In the case of an acute gout attack, colchicines, nonsteroidal anti-inflammatory drugs (NSAIDs), and glucocorticoids are the drugs mainly used. In the elderly population, one must take into account the possibility of GI complications from the above medications. To reduce these risks, intra-articular steroids, ice packs, and low-dose colchicine are more often used. In patients with recurrent gout attacks, chronic medication therapy can be used to maintain serum uric acid levels below 5 mg/dL. The maintenance therapy is usually with either probenecid, which increases the urinary excretion of uric acid, or allopurinol, which reduces the production of uric acid.

A **septic joint requires surgery** for drainage of infectious material followed by IV antibiotics. Methicillin-resistant *Staphylococcus aureus* (MRSA) will

usually require vancomycin, but coverage with antibiotics is dependent on the specific organisms isolated.

Degenerative joint disease treatment involves mobility exercises, maintenance of adequate range of motion, and weight loss, if appropriate. Intra-articular corticosteroid injections may provide relief for varying amounts of time, but should only be done every 4 to 6 months so as to avoid cartilage destruction. Surgery, such as joint replacement, is usually reserved for people with severe disease that affects their daily functions.

Therapy for rheumatoid arthritis involves multiple modalities. Education and counseling of the patient regarding disease progression, treatment options, and implications to lifestyle is essential. Exercises, such as those that maintain joint mobility and muscle strength, are very important, as the natural course of RA is to develop a stiff joint that becomes disabling. Physical therapy and occupational therapy are important to address specific areas in which the patient may need additional devices to perform activities of daily living.

Many different categories of medications are used in RA. These include NSAIDs, glucocorticoids, **disease-modifying antirheumatic drugs (DMARDs), anticytokines, and topical analgesics.** Among the DMARDs are sulfasalazine and methotrexate. Infliximab and etanercept are examples of anticytokine agents. Treatment regimens are individualized, and will often include a combination of two or three of these agents. Although effective, monitoring for hepatotoxicity must be performed.

Comprehension Questions

3.1 A 26-year-old man presents with a fever, dysuria, and left knee pain. He reports being sexually active with a new partner as recently as two weeks ago. On physical examination he is febrile and his left knee is erythematous, swollen, and tender. He denies a previous history of arthritis. Which of the following is the next best step?

A. CBC with differential
B. X-ray of the knee
C. Aspiration of synovial fluid
D. Serum uric acid level

3.2 A 44-year-old woman as a 5-month history of malaise and stiff hands in the morning that improve as the day goes by. She notes that both hands are involved. Which of the following treatments is most likely to lead to the best long term disease outcome for this patient?

A. Allopurinol
B. Ibuprofen
C. Naproxen
D. Methotrexate
E. Intravenous ceftriaxone

3.3 A 52-year-old man complains of bilateral knee pain for about 1 year. He is noted to have a BMI of 40 kg/m^2. Which of the following is the best therapy?
A. Allopurinol
B. Ibuprofen
C. Methotrexate
D. Intravenous ceftriaxone
E. Oral glucocorticoids

3.4 A 35-year-old man with hypertension presents with the sudden onset of right big toe pain. Which of the following is the best treatment?
A. Ipuprofen
B. Methotrexate
C. Colchicine
D. Intravenous antibiotics

ANSWERS

3.1 **C.** Infectious arthritis would need to be high on the differential diagnosis because of the danger of gonococcal arthritis. The history supports this diagnosis. This patient needs a joint aspiration to look for gram negative diplococci, crystals, and to obtain a sample for culture. He will likely require surgical drainage of the swollen joint and IV antibiotic therapy.

3.2 **D.** Morning stiffness, involvement of the hands, and symmetric arthritis are three of the criteria necessary for the diagnosis of rheumatoid arthritis. DMARD therapy, such as the use of methotrexate, would be indicated. Methotrexate as a disease-modifying agent would alter the natural history of the disease rather than just treat the symptoms.

3.3 **B.** Obesity is a risk factor for osteoarthritis, which is common in the knees and typically presents with a gradual onset and worsening of symptoms. Along with exercise and efforts to lose weight, an NSAID medication, such as ibuprofen, may provide symptomatic relief.

3.4 **C.** Gouty arthritis often initially presents in the big toe ("podagra") and the use of HCTZ, a common treatment for hypertension, also can increase the risk. Colchicine can provide effective acute treatment.

Clinical Pearls

- A red, swollen joint **must** be aspirated to rule out a joint infection.
- Trauma, infection, and crystals are the most common causes of acute monoarthritis in adults.

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Case 4

A 22-year-old woman who has never been pregnant before presents to you after having a positive home pregnancy test. She has no significant medical history. Upon further questioning, she states that she is unsure of the date of her last menstrual period. She denies any symptoms and is worried as she has not felt the baby move thus far. She is also concerned as she recently had dental x-rays taken prior to discovering that she was pregnant. Patient denies the use of any drugs, alcohol, or tobacco. She inquires about when she can get an ultrasound and a genetic test to rule out Down syndrome.

- When is an ultrasound indicated in prenatal care?
- What laboratory studies are routinely indicated at an initial prenatal visit?
- What is the risk to the pregnancy based on the radiation exposure that the patient has encountered?
- When is the optimal time for screening with a trisomy screen test?

ANSWERS TO CASE 4:
Prenatal Care

Summary: A 22-year-old primigravida woman with no significant past medical history presents for initial prenatal care visit. She has numerous questions regarding her care and recently has had dental x-rays taken.

- **Indications for an ultrasound in pregnancy:** According to the American College of Obstetricians and Gynecologists (ACOG), an ultrasound is not mandatory in routine, low-risk prenatal care. An ultrasound is indicated for the evaluation of uncertain gestational age, size/date discrepancies, vaginal bleeding, multiple gestations, or other high-risk situations.
- **Laboratory studies recommended at the initial prenatal visit:** Complete blood count (CBC), hepatitis B surface antigen (HBsAg), HIV testing, syphilis screening with a rapid plasma reagin (RPR), urinalysis and urine culture, rubella antibody, blood type and Rh status with antibody screen, Papanicolaou (Pap) smear, and cervical swab for gonorrhea and *Chlamydia.*
- **Risk to the pregnancy based on the radiation exposure from dental x-rays:** Risk for the baby is increased once the radiation exposure is greater than 5 rads; the radiation exposure from routine dental x-rays is 0.00017 rads.
- **The optimal time for the trisomy screen:** The optimal time is 16- to 18-week gestation; however, it may be performed between 15- and 20-week gestation, if necessary. Emerging evidence shows first trimester screening may be as effective in some centers.

ANALYSIS

Objectives

1. Learn the components of the preconception counseling and the initial prenatal visit.
2. Know the recommended screening tests and visit intervals in routine prenatal care.
3. Learn the relevant psychosocial aspects of providing prenatal care, including important counseling issues.

Considerations

Prenatal, or antenatal, care affords the opportunity to both perform appropriate medical testing and provide counseling and anticipatory guidance. Pregnancy

can be a time of anxiety and patients frequently have many questions. One of the goals of prenatal care is to provide appropriate education in order to help reduce anxiety and help women to be active participants in their own care.

APPROACH TO Prenatal Care

DEFINITIONS

ADVANCED MATERNAL AGE: Pregnant woman who will be 35 years or beyond at the estimated date of delivery.

ISOIMMUNIZATION: The development of specific antibodies as a result of antigenic stimulation by material from the red blood cells of another individual. For example, Rh isoimmunization means a Rh negative woman who develops anti-D (Rh factor) antibodies in response to exposure to Rh (D) antigen.

ASYMPTOMATIC BACTERIURIA: 100,000 cfu/mL or more of a pure pathogen of a mid-stream voided specimen.

GENETIC COUNSELING: An educational process provided by a health-care professional for individuals and families who have a genetic disease or who are at risk for such a disease. It is designed to provide patients and their families with information about their condition or potential condition and help them make informed decisions.

VERTICAL TRANSMISSION: Infectious passage of infection from mother to fetus, whether in utero, during labor and delivery, or postpartum.

ANTENATAL TESTING: A procedure that attempts to identify whether the fetus is at risk for uteroplacental insufficiency and perinatal death. Some of these tests include nonstress test and biophysical profile.

CLINICAL APPROACH

Preconception

In the United States, the first visit for prenatal care frequently is at 8 weeks of gestation or later, and yet it is the time preceding this that poses the greatest risk to fetal development. **A preconception visit is an ideal opportunity for the patient to discuss with her physician any issue related to possible pregnancy or contraception occurring within 1 year of pregnancy.** The preconception visit can be included during visits for many reasons, including fertility problems, contraception, periodic health assessment, recent amenorrhea or specifically for preconception counseling. Roughly one-half of patients with a negative pregnancy test may have some risk that could adversely affect a future pregnancy.

Because roughly 50% of pregnancies are unplanned or unintended, physicians should consider the potential of pregnancy when writing each prescription.

Women who intend to become pregnant should be advised to avoid, whenever possible, potentially harmful agents such as radiation, drugs, alcohol, tobacco, over-the-counter (OTC) medications, herbs, and other environmental agents. **Radiation exposure greater than 5 rads is associated with fetal harm. Most commonly performed x-ray procedures, including dental, chest, and extremity x-rays, expose a fetus to only very small fractions of this amount of radiation.** Fetuses are particularly sensitive to radiation during the early stages of development, between 2 and 15 weeks after conception. Whenever possible, the abdomen and pelvis should be shielded and x-rays performed only when the benefit outweighs the potential risk. Magnetic resonance imaging studies have not been proven to cause harm, but are not recommended in pregnancy, if avoidable. Ultrasound has not been shown to be harmful.

Women should refrain from OTC medicines, herbs, vitamins, minerals, and nutritional products until cleared by their obstetric provider. They should also be instructed to start a folic acid supplement at least 1 month prior to attempting to conceive. **For low-risk women, 400 μg of folic acid daily is recommended to reduce the risk of neural tube defects.** Higher doses are recommended in the presence of certain risk factors. For women with diabetes mellitus or epilepsy, 1 mg of folic acid a day is recommended. **A woman who has had a child with a neural tube defect should take 4 mg of folic acid daily.**

Women from certain ethnic backgrounds may be offered specific genetic screening. African and African-American women may be offered sickle cell trait screening. A French-Canadian or Ashkenazi Jewish background is an indication to consider screening for a Tay-Sachs carrier state. Southeast Asian and Middle Eastern women may be offered screening for thalassemia. Ashkenazi Jews and Caucasian women may be offered screening for cystic fibrosis.

Women who will be 35 years old or older at the anticipated time of delivery should be educated about age-related risk, particularly the increased risk of Down syndrome. They should be counseled about the available screening and diagnostic testing available, along with the appropriate time frame in which each test may be performed.

Women with medical conditions such as diabetes, asthma, thyroid disease, hypertension, lupus, thromboembolism, and seizures should be referred to providers with experience in managing high-risk pregnancies. Women with psychiatric disorders should be comanaged with a psychiatrist and counselor/therapist so that the patient can benefit from pharmacologic and behavioral therapy. These patients may require more frequent visits. Patients who have drug, tobacco, or alcohol dependence should be educated about the risks and referred to rehab/treatment centers to quit the drug prior to conception. Women should also be educated about proper nutrition and exercise during pregnancy. Preconception counseling may also address issues such as financial readiness, social support during pregnancy and the postpartum period, and issues of domestic violence.

Initial Prenatal Visit

The initial visit should address all the concepts in the preconception visit, if no preconception counseling was done. Ideally, the initial visit should be in the first trimester. A detailed history and physical examination, initial obstetric labs, and counseling regarding the logistics for prenatal care should be done at this visit. The history should begin with an assessment of the last menstrual period (LMP) and its reliability. **One of the most crucial pieces of information is the accuracy of the dating.** The first day of the LMP is used to obtain the estimated delivery date using Naegele's rule (from the first day of the LMP subtract 3 months and add 7 days). The LMP is considered reliable if the following criteria are met: the date is certain, the last menstrual period was normal, there has been no contraceptive use in the past 1 year, the patient has had no bleeding since the LMP, and her menses are regular. If these criteria are not met, an ultrasound should be performed. ACOG has established further criteria that can be used to ensure that a fetus is mature at the time of delivery, which include criteria such as early sonography and the timing of the positive pregnancy test.

History should also be obtained with particular attention to medical history, prior pregnancies, delivery outcomes, pregnancy complications, neonatal complications, and birth weights. Gynecologic history should focus on the menstrual history, contraceptive use, and history of sexually transmitted diseases (STDs). Allergies, current medications—both prescription and OTC—and substance use should also be investigated. Social history should consider whether the pregnancy was planned, unplanned, or unintentional. A discussion of social supports for the patient during the prenatal and postpartum period is also warranted. Genetic history should be obtained for the patient and partner's family, if known.

The initial examination should be thorough and should assess height, weight, blood pressure, thyroid, breast, and general physical and pelvic examinations. Pregnancy-specific examinations, including an estimation of gestational age by uterine size or fundal height measurement and an attempt to hear fetal heart tones by Doppler fetoscope should be performed. Heart tones should be obtainable by 10-week gestation using a handheld Doppler fetoscope. Pelvimetry has been removed as a recommended required intervention, but it may be useful to have a subjective assessment for risks of problems during delivery.

The initial laboratory screen (see Table 4–1) should include blood type and Rh status antibody screen, rubella status, HIV, hepatitis B surface antigen, rapid plasma reagin (RPR), urinalysis, urine culture, Pap smear, cervical swab for gonorrhea and *Chlamydia*, and a CBC.

The logistics of the prenatal visits should be addressed. A typical protocol includes follow-up visits every 4 weeks until 28-week gestation, every 2 weeks from 28- to 36-week gestation, and every week from 36-week gestation until delivery. More frequent visits should be performed if any problems arise or if all issues are not addressed in the scheduled visits.

Table 4–1 SUMMARY OF PRENATAL LABORATORIES, RAMIFICATIONS, AND EVALUATION

LAB TEST	FINDING	RAMIFICATIONS	NEXT STEP	COMMENTS
Hemoglobin	<10.5 g/dL	Preterm delivery Low fetal iron stores Identify thalassemia	Mild: therapeutic trial of iron Moderate: ferritin and Hb electrophoresis	
Rubella	Negative	Nonimmune to rubella	Stay away from sick individuals, vaccinate postpartum	Live attenuated vaccine in the postpartum period
Blood type	Any type	May help pediatricians identify ABO incompatibility		
Rh factor	Negative	May be susceptible to Rh disease	If antibody screen negative, give Rh_0GAM at 28 weeks, and if baby is Rh+, then also after delivery	
Antibody screen	Positive	May indicate isoimmunization	Need to identify the antibody, and then titer	Lewis lives, Kell kills, Duffy dies
HIV ELISA	Positive	May indicate infection with HIV	Western blot or PCR, if positive then place pt on anti-HIV meds, offer elective cesarean, or IV ZDV in labor	Intervention reduces vertical transmission from 25% to 2%
RPR	Positive	May indicate syphilis	Specific antibody such as MHA-TP, and if positive then stage disease	Less than 1 y, Penicillin × 1; >1 y or unknown, penicillin IM each week × 3

Table 4–1 SUMMARY OF PRENATAL LABORATORIES, RAMIFICATIONS, AND EVALUATION (CONTINUED)

LAB TEST	FINDING	RAMIFICATIONS	NEXT STEP	COMMENTS
Gonorrhea	Positive	May cause preterm labor, blindness	Ceftriaxone IM	
Chlamydia	Positive	May cause neonatal blindness, pneumonia	Azithromycin or amoxicillin orally	
Hepatitis B surface antigen	Positive	Patient is infectious	Check LFT's and hepatitis serology to determine if chronic carrier vs active hepatitis	Baby needs HBIG and hepatitis B vaccine
Urine culture	Positive	Asymptomatic bacteriuria may lead to pyelo 25%	Treat with antibiotic and recheck urine culture	If GBS is organism, then give penicillin in labor
Pap smear	Positive	Only invasive cancer would alter management	ASC-US = repap postpartum; LGSIL, HSIL = colposcopy	Reflexive HPV not recom–mended with ASC-US
Nuchal translucency (NT) (11-13 wk)	Positive	May indicate trisomy	Offer karyotype and follow-up ultrasounds	Increased NT means increased risk, not definitive diagnosis
Trisomy screen (16-20 wk)	Positive	At risk for trisomy or NTD	Basic ultrasound for dates; if dates confirmed offer genetic amniocentesis	Most common reason for abnormal serum screening: wrong dates

(*Continued*)

Table 4–1 SUMMARY OF PRENATAL LABORATORIES, RAMIFICATIONS, AND EVALUATION (CONTINUED)

LAB TEST	FINDING	RAMIFICATIONS	NEXT STEP	COMMENTS
1-h diabetic screen (26-28 wk)	Positive (elevated)	May indicate gestational diabetes	Go to 3-h GTT	About 15% of those screened will be positive
3-h glucose tolerance test	2 abnormal values	Gestational diabetes	Try ADA diet, monitor blood sugars, if elevated may need meds or insulin	About 15% of abnormal 1-h GCT will have gestational diabetes
GBS culture (35-37 wk)	Positive	GBS colonizing genital tract	Penicillin during labor	Helps to prevent early GBS sepsis of newborn

Abbreviations: ELISA, enzyme-linked immunosorbent assay; PCR, polymerase chain reaction; ASC-US, atypical squamous cell of uncertain significance; LGSIL, low grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion. *Reproduced with permission from Toy EC et al. Case Files:* Obstetrics and Gynecology, *3rd ed. New York: McGraw-Hill, 2009.*

The **ACOG does not stipulate routine ultrasonography in patients without complications.** Ultrasound is considered accurate for establishing gestational age, fetal number, viability, and placental location. Therefore, ultrasonography should be performed in patients without reliable dating criteria, with a discrepancy between the measured and expected uterine growth, and in case of a postdated pregnancy, suspicion for twin gestation, suspicion for placental issues, chromosomal abnormalities, or other problems. For gestational age estimations, ultrasonography is accurate for within 1 week if performed in the first trimester, 2 weeks in the second trimester, 3 weeks in the third trimester. If the ultrasound dates and LMP are off by more than the aforementioned intervals, the due date should be recalculated based on the ultrasound findings.

The visit should end with an adequate explanation of all patient/partner concerns. Women should be counseled that sexual activity is not associated with any harm during an uncomplicated pregnancy, although there may be conditions that arise during the course of a pregnancy that would make sexual activity inadvisable. A follow-up visit should be scheduled prior to her leaving the office. She should also be educated about preterm labor precautions,

signs of ectopic pregnancy, and situations in which to call the physician or go to the obstetrics triage unit for evaluation.

Subsequent Visits

At follow-up prenatal visits, concerns or questions brought up by the patient should be addressed. The examiner should ask questions specifically targeted at symptoms suggestive of complications that include gestational hypertension, preeclampsia, infections (urinary tract, vaginal, etc), fetal compromise, placenta previa/abruption, and preterm labor or premature rupture of membranes. At each visit, the patient should be asked about vaginal bleeding, loss of fluid, headaches, visual changes, abdominal pain, dysuria, facial or upper-extremity edema, vaginal discharge, and subjective sensation of fetal movements.

The examination on each subsequent visit should include weight, blood pressure, fundal height measurement, and fetal heart tones by hand-held Doppler. In addition, a urinalysis should be performed at every visit to assess for protein, glucose, or infection.

Subsequent Testing and Laboratory Studies

At 15 to 20 weeks' gestation (preferably between 16 and 18 weeks' gestation) a multiple marker test, which screens for Trisomy 21, Trisomy 18, and neural tube defects, should be offered to patients. The two most common modalities of screening the fetus for these anomalies are the triple screen and the quad screen. The triple screen tests for serum human chorionic gonadotropin (hCG), unconjugated estriol, and α-fetoprotein; the quad screen tests for those three plus inhibin-A. **The triple screen has a sensitivity of approximately 65% to 69% and specificity of 95% for detecting aneuploidy.** The quad screen increases sensitivity to approximately 80% without reducing specificity. The most common cause for a false-positive serum screen is incorrect gestational age dating. In some centers, fetal nuchal translucency can be measured by ultrasonography combined with maternal serum analyte levels (ie, free hCG and pregnancy-associated plasma protein A [PAPP-A]). This testing can be performed at 10- to 14-week gestation. Sensitivity and specificity of these tests is determined by the risk cutoff used (eg, for trisomy 21, sensitivity is 85.2% when specificity is 90.6%; at 95% specificity, the sensitivity is 78.7%). Women should be counseled about the limited sensitivity and specificity of the tests, the psychological implications of a positive test, the potential impact of delivering a child with Down syndrome, the risks associated with prenatal diagnosis and second-trimester abortion, and delays inherent in the process.

Women at increased risk of aneuploidy should be offered prenatal diagnosis by amniocentesis or chorionic villus sampling (CVS). Persons at increased

risk include women who will be older than 35 years at delivery and who have a singleton pregnancy (older than 32 years at delivery for women pregnant with twins); women carrying a fetus with a major structural anomaly identified by ultrasonography; women with ultrasound markers of aneuploidy (including increased nuchal thickness); women with a previously affected pregnancy; couples with a known translocation, chromosome inversion, or aneuploidy; and women with a positive maternal serum screen. Amniocentesis may be performed after 15-week gestation and is associated with a 0.5% risk of spontaneous abortion. CVS is performed at 10- to 12-week gestation and has a 1% to 1.5% risk of spontaneous abortion. CVS may be associated with transverse limb defects (1 per 3000 to 1 per 1000 fetuses). Women undergoing CVS also should be offered maternal serum α-fetoprotein testing for neural tube defects. Women older than age 35 years at time of delivery may opt for serum screening and ultrasonography before deciding whether to proceed with amniocentesis. **Although the risk for trisomy 21 increases with maternal age, an estimated 75% of affected fetuses are born to mothers younger than age 35 years at time of delivery.**

The ACOG and the American Diabetes Association recommend that all pregnant women be screened for gestational diabetes at 24 to 28 weeks' gestation, except women who are at low risk (eg, younger than age 25 years, belonging to a low-risk ethnic group, normal prepregnancy weight, no history of abnormal glucose metabolism, no previous poor obstetric outcomes, and no first-degree relatives with diabetes). Screening is standard in the United States, with 94% of physicians reporting universal screening.

At 24 to 28 weeks' gestation, patients should be screened for gestational diabetes with a 1-hour 50 g glucose challenge test. Most guidelines consider a value above 140 mg/dL as abnormal, whereas new studies advocate using a value of 135 mg/dL. A value of 200 mg/dL or greater is generally diagnostic of gestational diabetes. When the screening test is positive, a 3-hour glucose tolerance test (GTT) should be performed (after an overnight fast) by giving the patient a 100-g glucose load and obtaining fasting, 1-hour, 2-hour, and 3-hour postload serum glucose samples; two out of four positive values generally establishes the diagnosis of gestational diabetes. A diagnosis of gestational diabetes impacts the pregnancy, but also increases the risk of type II diabetes in the patient throughout her life.

At 28 weeks' gestation, a repeat RPR and hemoglobin/hematocrit should be obtained in those at risk for syphilis and anemia, respectively. In addition, a patient who is Rh-negative should receive Rh_O(D) immune globulin (Rh_OGAM) at this time. An Rh-negative patient should also receive Rh_O(D) immune globulin at delivery and in any instance of trauma. Nonsensitized, Rh-negative women also should be offered a dose of Rh_O(D) immune globulin after spontaneous or induced abortion, ectopic pregnancy termination, CVS, amniocentesis, cordocentesis, external cephalic version, abdominal trauma, and second- or third-trimester bleeding. Administration of Rh_O(D) immune

globulin can be considered before 12-week gestation in women with a threatened abortion and live embryo, but Rh alloimmunization is rare.

The Centers for Disease Control and Prevention and ACOG recommend that **all women be offered group B *Streptococcus* (GBS) screening by vaginorectal culture at 35 to 37 weeks' gestation** and that colonized women be treated with intravenous antibiotics at the time of labor or rupture of membranes in order to reduce the risk of neonatal GBS infection. The **proper method of collection is to swab the lower vagina, perineal area, and rectum.** Of tested women, 10% to 30% will test positive for GBS colonization. Because GBS bacteriuria indicates heavy maternal colonization, women with GBS bacteriuria at any time during their pregnancy should be offered intrapartum antibiotics and do not require a vaginorectal culture. Similarly, women with a previous infant who was diagnosed with a GBS infection should be offered intrapartum antibiotics.

If a patient does not go into labor spontaneously by 42 weeks' gestation, induction of labor should be considered to reduce the risk of neonatal mortality and morbidity. Several studies have shown reduced risks with induction at 41 weeks' gestation. ACOG recommends testing for fetal well-being in prolonged pregnancies, starting in the 42nd week of gestation.

Vaccinations During Pregnancy

Women who will be in their third trimester during flu season should be offered the influenza vaccine. Influenza vaccine is safe in any stage of pregnancy provided there is no allergy to any of its components. Tetanus toxoid vaccination can also be given safely during pregnancy. Varicella and rubella vaccinations are not advised during pregnancy. For pregnant mothers with a rubella nonimmune status, a rubella vaccination should be given after delivery of the infant.

Comprehension Questions

4.1 A 24-year-old woman presents for an initial prenatal visit. She is at 9-week gestation based on her LMP but, on further questioning, she is not certain of the first day of her LMP. Which of the following would be the most accurate estimate of her gestational age?

A. Using her LMP if her uterine size is consistent
B. A first trimester ultrasound
C. A second trimester ultrasound
D. A quantitative serum hCG level

4.2 A 38-year-old pregnant woman presents for initial visit at 12-week gestation. She requests a "genetic screen" because she is concerned about her advanced maternal age. She does not want any invasive testing that may cause a potential miscarriage. Which of the following is most appropriate to offer this patient?

A. If no prior personal or family history of genetic defects, no screen is needed.
B. Draw and send blood for the triple or quad screen, as patient has advanced maternal age.
C. Nuchal translucency screening and hCG and Pregnancy Associated Pregnancy Protein A (PAPP-A) testing.
D. Offer the patient chorionic villus sampling.

4.3 A 28-year-old woman with a history of epilepsy presents for a preconception consultation visit. Which of the following is the most important advice to give to this patient?

A. Diabetes screening prior to pregnancy.
B. EEG reading that is normal prior to conception.
C. Preconception folate supplementation.
D. Stop epilepsy medication prior to pregnancy and through the first trimester.

4.4 A 28-year-old G1 P0 woman at 16-week gestation is noted to be Rh negative. Which of the following is the most appropriate next step for this patient?

A. Administer Rh_0GAM at this time.
B. Check the patient's antibody screen (indirect Coombs).
C. Schedule the patient for amniocentesis to assess for isoimmunization.
D. Counsel the patient to terminate the pregnancy.

ANSWERS

4.1 **B.** A first trimester ultrasound is accurate to within ±1 week for gestational dating and would be the most accurate assessment of gestational age of the options listed.

4.2 **C.** In the 11- to 13-week gestational age, first trimester trisomy screening may be performed by ultrasound looking at a echolucent area behind the fetal neck called the nuchal translucency. That measurement together with serum hCG and PAPP-A can give a risk for trisomy.

4.3 **C.** Women with a history of epilepsy should receive 1 mg of folic acid supplementation daily to help prevent neural tube defects. In general epilepsy medications should be continued, although the type of medication may be changed. For instance, valproic acid has a relatively high rate of neural tube defects associated with its use, and if possible, another medication should be used.

4.4 **B.** For women who are Rh negative, the next step is to assess the antibody screen or indirect Coombs test. If the antibody screen is negative, there is no isoimmunization, and Rh_OGAM is given at 28-week gestation and again at delivery if the baby is confirmed as Rh positive. The Rh_OGAM is given to prevent isoimmunization. If the antibody screen is positive and the identity of the antibody is confirmed as Rh (anti-D), then assessment of its titer will assist in knowing the probability of fetal effect. A low titer can be observed, whereas a high titer should initiate further testing such as ultrasound and possibly amniocentesis.

Clinical Pearls

- The initial prenatal visit often is scheduled after fetal organogenesis has occurred. For this reason, a preconception visit can be very beneficial. Furthermore, when prescribing medications, physicians must consider the possibility that any woman of reproductive age may become pregnant.
- Genetic counseling should be offered to any woman who *will be* 35 years old or older at her estimated date of confinement (EDC).
- Folic acid supplementation is important for every woman, and the recommended daily dose is based on individual risk factors such as anticonvulsant therapy or a previous pregnancy with a neural tube defect.
- If all criteria are met, Naegele's rule can be used to determine the EDC (subtract 3 months, add 7 days). If there is any uncertainty, the dating should be confirmed by ultrasound, preferably in the first trimester.

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Case 5

A 6-month-old male child is brought to your office by his mother for a routine well-child visit. His mother is concerned that he is not yet saying "mama," because her best friend's baby said mama by age 6 months. Your patient was born to a full-term, uncomplicated pregnancy to a 23-year-old G1P1 mother. He was delivered by a spontaneous vaginal delivery and there were no complications in the neonatal period. You have been following him since his birth. He has had appropriate growth and development up to this age and is up-to-date on his routine immunizations. He had one upper respiratory infection at age 5 months that was treated symptomatically. There is no family history of any developmental, hearing, or speech disorders. He has been fed since birth with an iron-fortified infant formula. Cereals and other baby foods were added starting at age 4 months. He lives with both parents, neither of whom smokes cigarettes.

On examination, he is a vigorous infant who is at the 50th percentile for length and weight and 75th percentile for head circumference. His physical examination is normal. On developmental examination, he is seen to sit for a short period of time without support, reach out with one hand for your examining light, pick up a Cheerio with a raking grasp and put it in his mouth, and he is noted to babble frequently.

- What immunizations would be recommended at this visit?
- By what age should an infant say "mama" and "dada"?
- The child's mother asks when she can place him in front-facing car seat. What is your recommendation?

ANSWERS TO CASE 5:
Well-Child Care

Summary: A 6-month-old healthy child is brought in for a routine well-child examination.

- **Recommended immunizations for a 6-month well-child visit (in a child who is up-to-date on routine immunizations):** *Diphtheria, tetanus,* and acellular *pertussis* (DTaP) no. 3, hepatitis B no. 3, *Haemophilus influenzae* type b (Hib) no. 3 and rotavirus no. 3; inactivated polio vaccine no. 3 can be given between 6 and 15 months of age.
- **Age by which a child should say "mama" and "dada":** Most children will start to say "dada" or "mama" nonspecifically between ages 6 and 9 months. It usually becomes specific between ages 8 and 12 months.
- **Recommendations for continuing in a rear-facing car seat:** A child should stay in a rear-facing car seat until the child weighs at least 20 lb and is at least 1 year old.

ANALYSIS

Objectives

1. Learn the basic components of a well-child examination.
2. Know the routine immunization schedule for children.
3. Know common developmental milestones for young children.

Considerations

The pediatric well-child examination serves many valuable purposes. It provides an opportunity for parents, especially first-time parents, to ask questions about, and for the physician to address specific concerns regarding, their child. It allows the physician to assess the child's growth and development in a systematic fashion and to perform an appropriate physical examination. It also allows for a review of both acute and chronic medical conditions. When performed at recommended time intervals, it gives the opportunity to provide age-appropriate immunizations, screening tests, and anticipatory guidance. Finally, it supports the development of a good doctor-patient-family relationship, which can promote health and serve as an effective tool in the management of illness.

APPROACH TO
Well-Child Examination

DEFINITIONS

AMBLYOPIA: Reduction in loss of vision in one eye from lack of use. Strabismus is the most common cause of amblyopia.

STRABISMUS: Ocular misalignment.

CLINICAL APPROACH

Pediatric History

For the purposes of routine well-child visits, a comprehensive history should be obtained at the initial visit with more focused, interval histories obtained at subsequent encounters. The initial history should include an opportunity for the parent to raise any questions or concerns that the parent may have. New parents, especially first-time parents and young parents, often have many questions or anxieties about their child. The ability to discuss them with the physician will help to engender a positive physician-patient-family relationship and improve the parent's satisfaction with their child's care.

A complete past medical history should be obtained. This should start with a detailed prenatal and pregnancy history, including the duration of the pregnancy, any complications of pregnancy, any medications taken, the type of delivery performed, the child's birth weight, and any neonatal problems. Any significant chronic or acute illnesses should be recorded. The use of any medications, both prescription and over-the-counter, should be reviewed.

A detailed family history, including information (when available) on both maternal and paternal relatives should be obtained. A thorough social history is critical in pediatric care. Information, including the parents' education levels, relationships, religious beliefs, use of substances (tobacco, alcohol, drugs) and socioeconomic factors can provide significant insight into the health and development of the child.

Efforts should be made to obtain old medical records, if any are available. Growth charts, immunization records, results of screening tests, and other valuable information that can assist with the child's assessment and reduce the unnecessary duplication of previously performed interventions can often be found.

Growth

At each well-child visit, the child's height and weight should be recorded and plotted on a standard growth chart. Head circumference is measured and plotted in children 3 years of age and younger. Children older than age 3 years

should have their blood pressure recorded using an appropriate-size pediatric cuff. Significant variances from accepted, age-adjusted, population norms, or growth that deviates from predicted growth curves, may warrant further evaluation. **Failure to thrive** is defined by some as weight below the third or fifth percentile for age, and by others as decelerations of growth that have crossed two major growth percentiles in a short period of time. Either significant loss or gain of weight may prompt an in-depth discussion of nutrition and caloric intake.

Development

An assessment of the child's development in the areas of **gross motor, fine motor/adaptive, language, and social/personal** skills is an important aspect of each well-child visit. Numerous screening tools, such as the Denver II developmental screening test, the Parents' Evaluations of Developmental Status (PEDS), and others, are available to assist with these assessments. These assessments typically involve both responses from the parents regarding the child's behavior at home and observations of the child in the office setting. Persistent delays in development, either globally or in individual skill areas, should prompt a more in-depth developmental assessment, as early intervention may effectively aid in the management of some developmental abnormalities. Table 5–1 summarizes many of the important motor, language, and social developmental milestones of early childhood.

Screening Tests

There are a variety of screening tests used to prevent disease and promote proper developmental and physical growth. These include tests for congenital diseases, lead screening, evaluating children for anemia, and hearing and vision screens.

Each state requires screening of all newborns for specified congenital diseases; however, the specific diseases for which screening is done vary from state to state. **All states require testing for phenylketonuria (PKU) and congenital hypothyroidism,** as early treatment can prevent the development of profound mental retardation. Diseases for which testing commonly occurs include hemoglobinopathies (including sickle cell disease), galactosemia, and other inborn errors of metabolism. This screening is done by collecting blood from newborns prior to discharge from the hospital. In some states, newborn screening is repeated at the first routine well visit, usually at about 2 weeks of age.

Nationwide, the prevalence of childhood lead poisoning has declined, primarily because of the use of unleaded gasoline and lead-free paints. However, in some communities, the risk of lead exposure is higher. Universal screening for lead poisoning is recommended by the Centers for Disease Control and Prevention and the American Academy of Pediatrics for children at ages 9 to 12 months and again at age 2 years in communities where 27% or more of

Table 5–1 DEVELOPMENTAL MILESTONES

AGE	MOTOR	LANGUAGE	SOCIAL	OTHER
1 mo	Reacts to pain	Responds to noise	Regards human face Establishes eye contact	
2 mo	Eyes follow object to midline Head up prone	Vocalizes	Social smile Recognizes parent	
4 mo	Eyes follow object past midline Rolls over	Laughs and squeals	Regards hand	
6 mo	Sits well unsupported Transfers objects hand to hand (switches hands) Rolls prone to supine	Babbles	Recognizes strangers	Mnemonic: Six strangers switch sitting at 6 mo
9 mo	Pincer grasp (10 mo) Crawls Cruises (walks holding furniture)	Mama/dada Bye-bye	Starts to explore	Can crawl, therefore can explore It takes 9 mo to be a "mama" Grabs furniture to walk
12 mo	Walks Throws object	1-3 words Follows 1-step commands	Stranger and separation anxiety	Walking away from mom causes anxiety Knows 1 word at 1 y

(*Continued*)

Table 5–1 DEVELOPMENTAL MILESTONES (CONTINUED)

AGE	MOTOR	LANGUAGE	SOCIAL	OTHER
2 y	Walks up and down stairs Copies a line Runs Kicks ball	2-3-word phrases 1/2 of speech is understood by strangers Refers to self by name Pronouns	Parallel play	Puts 2 words together at 2 At age 2, 2/4 ($^1/_2$) of speech understood by strangers
3 y	Copies a circle Pedals a tricycle Can build a bridge of 3 cubes Repeats 3 numbers	Speaks in sentences 3/4 of speech is understood by strangers Recognizes 3 colors	Group play Plays simple games Knows gender Knows first and last name	Tricycle, 3 cubes, 3 numbers, 3 colors, 3 kids make a group At age 3, $^3/_4$ of speech understood by strangers
4 y	Identifies body parts Copies a cross Copies a square (4.5 y) Hops on one foot Throws overhand	Speech is completely understood by strangers Uses past tense to speak of things that happened before Tells a story	Plays with kids, social interaction	Song "head, shoulder, knees, and toes," 4 parts reminds you that at age 4 can identify body parts At age 4, $^4/_4$ of speech is understood by strangers Uses past tense to speak of things that happened before

Table 5–1 DEVELOPMENTAL MILESTONES (CONTINUED)

AGE	MOTOR	LANGUAGE	SOCIAL	OTHER
				A 4-year-old can copy 2 lines to draw a cross and a square, which has 4 sides
5 y	Copies a triangle Catches a ball Partially dresses self	Writes name Counts 10 objects		
6 y	Draws a person with 6 parts Ties shoes Skips with alternating feet	Identifies left and right		Mnemonic–At 6 y: skips, shoes, person with parts

Modified with permission, from WW Hay, AR Hayword, MJ Levin, JM Sondheimer. Current Pediatric Diagnosis and Treatment. *17th ed. New York, NY: McGraw-Hill; 2005.*

homes were built before 1950 or where 12% or more of children have a venous lead concentration more than 10 μg/dL. In other communities, screening should be targeted to high-risk children (Table 5–2).

Iron deficiency is the most common cause of anemia in children. Iron-containing formula and cereals have helped to reduce the occurrence of iron deficiency. Children who drink more than 24 oz of cow's milk, have iron-restricted diets, or were low birth weight or preterm, or whose mother was iron deficient, are at higher risk. Iron deficiency can be evaluated by a hemoglobin or hematocrit measurement, usually taken between 6 and 12 months of age. Repeat testing can be considered annually, especially in high-risk children, up through the age of 5 years. An anemic child can empirically be given a trial of an iron supplement and dietary modification. Failure to respond to iron therapy should warrant further evaluation of other causes of anemia.

Most states now mandate newborn hearing screening by auditory brainstem response or evoked otoacoustic emission. All high-risk infants, regardless of

Table 5–2 ELEMENTS OF A LEAD RISK QUESTIONNNAIRE

Recommended questions

- Does your child live in or regularly visit a house built before 1950? This could include a day care center, preschool, the home of a babysitter or relative, and so on.
- Does your child live in or regularly visit a house built before 1978 with recent, ongoing, or planned renovation or remodeling?
- Does your child have a sister or brother, housemate, or playmate who is being followed for lead poisoning?

Questions that may be considered by region or locality

- Does your child live with an adult whose job (eg, at a brass/copper foundry, firing range, automotive or boat repair shop, or furniture refinishing shop) or hobby (eg, electronics, fishing, stained-glass making, pottery making) involves exposure to lead?
- Does your child live near a work or industrial site (eg, smelter, battery recycling plant) that involves the use of lead?
- Does your child use pottery or ingest medications that are suspected of having a high lead content?
- Does your child have exposure to burning lead-painted wood?

Reproduced, with permission, from Stead LG, Stead SM, Kaufman MS. First Aid for the Pediatrics Clerkship. *New York, NY: McGraw-Hill; 2004:39-40.*

requirement, should be screened. High-risk infants include those with a family history of childhood hearing loss, craniofacial abnormalities, syndromes associated with hearing loss (such as neurofibromatosis), or infections associated with hearing loss (such as bacterial meningitis). Older infants and toddlers can be assessed for hearing problems by questioning the parents or performing office testing by snapping fingers, or by using rattles or other noisemakers. Office-based audiometry can usually be performed in children aged 3 years and older. Any hearing loss should be promptly evaluated and referred for early intervention, if necessary.

Vision screening can also start in the newborn nursery. Evaluation of the neonate for red reflexes on ophthalmoscopy should be a standard part of the newborn examination. The presence of red reflexes helps to rule out the possibility of congenital cataracts and retinoblastoma. The evaluation of an older infant should include a subjective evaluation of the child's vision by the parent. Infants should be able to focus on a face by age 1 month and should move their eyes consistently and symmetrically by age 6 months. An examining light should reflect symmetrically off of both corneas; asymmetric light reflex may be a sign of strabismus. The cover-uncover test also is a screening examination for strabismus. The child focuses on an object with both eyes and the examiner covers one eye. Strabismus is suggested when the uncovered eye deviates to focus on the object. **Strabismus should be referred to a pediatric**

ophthalmologist as soon as it is detected, as early intervention results in a lower incidence of amblyopia. After the age of 3 years, most children can be tested for visual acuity using a Snellen chart, modified with a "tumbling E" or pictures, instead of letters.

Other screening tests may be recommended for high-risk children. Tuberculosis (TB) screening is recommended for children who were born or live in a region of high TB prevalence or who have close contact with someone known to have TB. The Mantoux test is the screening test of choice; the multiple puncture tine test is no longer recommended. Screening for hyperlipidemia in children is controversial but may be appropriate if there is a family history of hyperlipidemia or of premature coronary artery disease.

Anticipatory Guidance

A primary feature of the well-child visit should be education of the patient and family on issues that promote health and prevent illness, injury, or death. This anticipatory guidance should be focused and age appropriate. The use of preprinted handouts can reinforce issues discussed in the office, address issues that could not be discussed because of time limitations, and allow for the parent to review the information as needed at home. Subjects that should routinely be addressed include injury prevention, nutrition, development, discipline, exercise, mental health issues, and the need for ongoing care (eg, immunization schedules, future well-child visits, dental care).

Accidents and injuries are the leading cause of death in children older than age 1 year. Accidents involving motor vehicles, both traffic and pedestrian accidents, are the leading cause of these accidental deaths. All states now require the use of car safety seats for children, although the regulations vary from state to state. The general recommendation is that a child should be in the back seat of the vehicle whenever possible. If there is no back seat, the child should only ride in the front seat if there is no air bag or if the air bag can be disabled. **A child should sit in a rear-facing car seat until the child is both 1 year old and weighs at least 20 lb.** A child older than 1 year and between 20 and 40 lb should use a forward-facing car seat. When the child weighs more than 40 lb, the child may use a booster-type seat along with the lap and shoulder seatbelts. The child can stop using the booster when the child can sit with his or her back squarely against the back of the seat with the legs bent at the knees over the front of the seat. The child usually will need to be at least 4'9" in height and 8 to 12 years of age to meet these requirements. No child should ride in the front seat unless they are 13 years of age or older.

The leading cause of death of infants younger than 1 year of age is **sudden infant death syndrome** (SIDS). The Back To Sleep campaign advises parents to place their infant on the infant's back—not abdomen or side—when the infant is put down to sleep, as this reduces the risk of dying of SIDS. In addition, the infant should be placed on a firm mattress with nothing else in the

crib—this includes pillows, positioning devices, and toys. Heavy coverings and soft mattresses have been associated with an increased risk of SIDS.

As children get older, anticipatory guidance on other safety issues become important. As children learn to crawl and walk, stairwells should be blocked to reduce the risk of injuries from falling. Cleaning supplies, medications, and other potential poisons need to be stored safely out of reach of children, preferably in locked cabinets. Similarly, firearms should be stored safely, preferably unloaded and in locked cabinets or safes. Older children should be advised regarding the importance of wearing a helmet while riding a bicycle, skateboard, scooter, or other similar vehicle. All families should be advised to have smoke detectors throughout the home, especially in rooms where people sleep, and to keep the hot water heater set at or below 120°F to reduce the risk of scald injuries.

Nutrition is another important area of anticipatory guidance. Infants younger than 1 year old should be breast-fed or receive an iron-containing formula. Cereals and other baby foods can be introduced between 4 and 6 months of age. Whole cow's milk is introduced at 12 months and continued until at least the age of 2 years, before considering changing to reduced fat milk.

Immunizations

Ensuring that each child has received the child's age-appropriate immunizations is a key component of each well-child visit. The child's immunization status also should be reviewed at acute care visits. Minor illnesses, even those causing low-grade fevers, are not contraindications to vaccinating children, allowing an acute care visit to be an excellent opportunity to provide this service. **True contraindications to providing a vaccination include a history of an anaphylactic reaction to a specific vaccine or vaccine component or a severe illness,** with or without a fever. Figure 5–1 shows the recommended childhood vaccination schedule. Catch-up schedules for children who are either completely unimmunized or who have missed doses of the recommended vaccines are published by the Centers for Disease Control and Prevention.

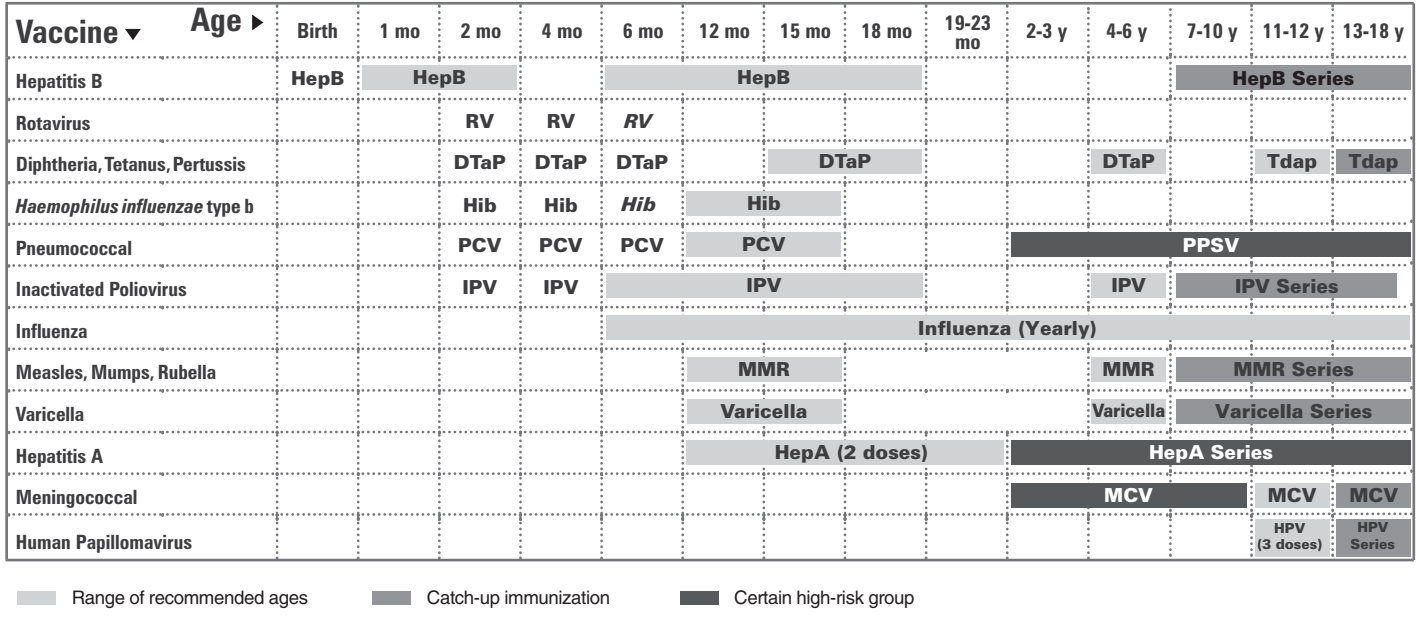

Figure 5–1. Recommended immunization schedule for persons aged 0 through 18 years—United States • 2009. For those who fall behind or start late, see the schedule below and the catch-up schedule. *Reproduced from the CDC.*

Comprehension Questions

5.1 A 7-month-old baby boy is brought into the office for a possible ear infection. In assessing the infant's posture, you note that he is not able to sit very well without support. You also observe other fine motor skills and speech. Which of the following is the most accurate statement?

A. By 3 months of age, a child should be able to sit up without support.
B. By 6 months of age, a child should be able to transfer objects from one hand to another.
C. By 9 months of age, a child should be able to walk.
D. By 12 months of age, a child should be able to put two words together.

5.2 A 5-year-old presents to your clinic for a school physical. The child weighs 42 lb and is up-to-date on his immunizations. Which of the following anticipatory guidances is most appropriate for a child at this age?

A. He should ride in a rear-facing car seat in the back seat of the vehicle.
B. He should ride in a forward-facing car seat in the back seat of the vehicle.
C. He should ride in a forward-facing car seat in the front seat of the vehicle.
D. He should ride in a booster seat in the back seat of the vehicle.

5.3 A 4-month-old infant is brought into the family physician's office for routine checkup and immunizations. Which of the following vaccines is routinely recommended at this time?

A. Diphtheria, tetanus, acellular pertussis (DTaP)
B. Oral polio vaccine (OPV)
C. Measles, mumps, rubella (MMR)
D. Varicella

5.4 A 5-year-old child is brought into the pediatrician's office for immunization and physical examination. The mother is concerned that her child is a little "under the weather." Which of the following is a contraindication to vaccinating the child?

A. Acute otitis media with a temperature of 100°F requiring antibiotic therapy
B. Previous vaccination reaction that consisted of fever and fussiness that lasted for 2 days
C. History of an allergic reaction to penicillin
D. Previous vaccination reaction that consisted of wheezing and hypotension

ANSWERS

5.1 **B.** It is critical to understand the normal milestones for gross motor, fine motor, speech and social categories. Delay in one or more areas can indicate problems which if addressed can alleviate long-term issues. Most 6-month-old children would be expected to sit without support. Six-month-old children would also be expected to transfer objects from one hand to the other, roll from a prone to supine position, babble, and recognize strangers.

5.2 **D.** A child who weighs more than 20 lb and is older than 1 year of age may sit in a forward-facing car seat in the back seat of the car. A child who weighs more than 40 lb is usually big enough to use a booster seat, also in the back seat of the car.

5.3 **A.** DTaP is routinely recommended at ages 2, 4, 6, and 12 to 15 months, and at 4 to 6 years of age. Oral polio vaccination is no longer routinely recommended in children; the inactivated, injectable polio vaccine is recommended in its place. MMR vaccination is recommended at ages 12 to 15 months and 4 to 6 years. Varicella vaccination is recommended at ages 12 to 15 months and 4 to 6 years.

5.4 **D.** A previous anaphylactic reaction is a true contraindication to vaccination. Minor illnesses or vaccination reactions, even with fever, are not contraindications. Penicillin is not a component of vaccines and history of allergy to this medication is not a contraindication.

Clinical Pearls

- True contraindications to providing vaccinations are rare; acute care visits are an excellent opportunity to provide childhood vaccinations.
- SIDS is the leading cause of death in infants younger than age 1 year. Parents should place their children on their "Back-to-Sleep."

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Case 6

A 35-year-old woman with a history of asthma presents to your office with symptoms of nasal itching, sneezing, and rhinorrhea. She states she feels this way most days but her symptoms are worse in the spring and fall. She has had difficulty sleeping because she is always congested. She states she has taken diphenhydramine (Benadryl) with no relief. She does not smoke cigarettes and does not have exposure to passive smoke but she does have two cats at home. On examination, she appears tired but is in no respiratory distress. Her vital signs are temperature, 98.8°F; blood pressure, 128/84 mm Hg; pulse, 88 beats/min; and respiratory rate, 18 breaths/min. The mucosa of her nasal turbinates appear swollen (boggy) and have a pale, bluish-gray color. Thin and watery secretions are seen. No abnormalities are seen on ear examination. There is no cervical lymphadenopathy noted and her lungs are clear.

- What is the most likely diagnosis?
- What is your next step?
- What are important considerations and potential complications of management?

ANSWERS TO CASE 6:
Allergic Disorders

Summary: A 35-year-old asthmatic woman complains of chronic nasal congestion that is worse in the spring and the fall.

- **Most likely diagnosis:** Allergic rhinitis.
- **Next step in management of this patient:** Treatment with antihistamines, decongestants, or intranasal steroids. These treatments can also be used in combination with each other.
- **Considerations and possible complications of therapy:**. Recognition and reduction of potential allergen exposure will yield more success in management than pharmacotherapy alone. Excessive use of topical decongestants can cause rebound congestion

ANALYSIS

Objectives

1. Understand the inflammatory nature of allergic rhinitis.
2. Recognition of physical examination findings consistent with allergic rhinitis.
3. Develop an approach to the management of allergic rhinitis, including the roles of pharmacotherapy and reduction of allergen exposure.
4. Recognition and management of asthma.
5. Identification of essential features and treatment of anaphylaxis.

Considerations

This patient presents with a classic history of allergic rhinitis. Her history of itchy eyes, nasal congestion and discharge, and seasonal in nature (worse in spring and fall) are all consistent with allergic rhinitis. Her examinations are also consistent with the diagnosis. Her mucosa of her nasal turbinates appear swollen (boggy) and have a pale, bluish-gray color. Thin and watery secretions are seen. The best therapy for this condition is avoidance of allergens, but due to the probable allergy to pollen, this would be difficult in this case. Nasal corticosteroids offer the most consistent symptomatic relief.

APPROACH TO Allergic Disorders

DEFINITIONS

ALLERGIC RHINITIS: Inflammation of the nasal passages caused by allergic reaction to airborne substances.

ANAPHYLAXIS: Rapidly progressing, life-threatening allergic reaction, mediated by IgE immediate hypersensitivity reaction.

CLINICAL APPROACH

Background

Rhinitis is inflammation of the nasal membranes and is characterized by any combination of the following: sneezing, nasal congestion, nasal itching, and rhinorrhea. The eyes, ears, sinuses, and throat can also be involved. Allergic rhinitis is the most common cause of rhinitis, occurring in up to 20% of the population.

Pathophysiology

Allergic rhinitis involves inflammation of the mucous membranes of the nose, eyes, eustachian tubes, middle ear, sinuses, and pharynx. Inflammation of the mucous membranes is characterized by a complex interaction of inflammatory mediators but, ultimately, is triggered by an immunoglobulin E (IgE)-mediated response to an extrinsic protein.

In susceptible individuals, exposure to certain foreign proteins leads to allergic sensitization, which is characterized by the production of specific IgE directed against these proteins. This specific IgE coats the surface of mast cells, which are present in the nasal mucosa. When the specific allergen is inhaled into the nose, it can bind to the IgE in the mast cells, leading to a delayed release of a number of mediators.

Mediators that are immediately released include histamine, tryptase, chymase, and kinase. Mast cells quickly synthesize other mediators, including leukotrienes and prostaglandin D_2. Symptoms can occur quickly after exposure. Mucous glands are stimulated, leading to increased secretions. Vasodilation occurs, causing congestion. Stimulation of sensory nerves leads to sneezing and itching. Other symptoms include the redness and tearing of eyes, postnasal drip, and ear pressure.

Over the next 4 to 8 hours, these mediators, through a complex interplay of events, recruit neutrophils, eosinophils, lymphocytes, and macrophages to the mucosa. These inflammatory cells cause more congestion and mucus production that may persist for hours or days. Systemic effects, including fatigue, sleepiness, and malaise, can result from the inflammatory response as well.

History

Obtaining a detailed history is important in the evaluation of allergic rhinitis, as specific triggers may be identified. Evaluation should include the nature, duration, and time course of symptoms. The recent use of medications is another important consideration. Other aspects include a family history of allergic diseases, environmental exposures, and comorbid conditions.

Part of the history should include the time pattern of symptoms and whether symptoms occur at a consistent level throughout the year (**perennial rhinitis**), only occur in specific seasons (**seasonal rhinitis**), or a combination of the two. Trigger factors, such as exposure to pollens, mold spores, specific animals, or cleaning of the house, can sometimes be identified. Irritant triggers, such as smoke, pollution, and strong smells can aggravate symptoms of allergic rhinitis. Response to treatment with antihistamines supports the diagnosis of allergic rhinitis.

Symptoms

Symptoms that can be associated with allergic rhinitis include sneezing, itching (of nose, eyes, or ears), rhinorrhea, postnasal drip, congestion, anosmia, headache, earache, tearing, red eyes, and drowsiness.

Physical Examination

Common findings on examination include "allergic shiners," which are dark circles around the eyes related to vasodilation or nasal congestion. The "nasal crease" can be seen in some cases. It is a horizontal crease across the lower half of the bridge of the nose caused by repeated upward rubbing of the tip of the nose by the palm of the hand ("allergic salute").

Examination of the nose may reveal mucosa of the nasal turbinates to be swollen (boggy) and have a pale, bluish-gray color. Assessment of the character and quantity of nasal mucus may be helpful in ascertaining a diagnosis. Thin and watery secretions are frequently associated with allergic rhinitis, whereas thick and purulent secretions are usually associated with sinusitis. The characteristic of the mucous is not always diagnostic, as thick, purulent, colored mucus can also occur with allergic rhinitis.

The nasal cavity should be inspected for growths such as polyps or tumors. Polyps are firm, gray masses that are often attached by a stalk, which may not be visible. After spraying a topical decongestant, polyps do not shrink, whereas

the surrounding nasal mucosa does shrink. Examine the nasal septum to look for any deviation or septal perforation that may be present as a consequence of chronic rhinitis, granulomatous disease, cocaine abuse, prior surgery, topical decongestant abuse, or, rarely, topical steroid overuse.

Otoscopy should be performed to look for tympanic membrane retraction, air-fluid levels, or bubbles. Performing pneumatic otoscopy can be considered to look for abnormal tympanic membrane mobility. These findings can be associated with allergic rhinitis, particularly if eustachian tube dysfunction or secondary otitis media is present. Ocular examination may reveal findings of injection and swelling of the palpebral conjunctivae, with excess tear production. Dennie-Morgan lines (prominent creases below the inferior eyelid) are associated with allergic rhinitis.

"Cobblestoning" of the posterior pharynx is often observed. This is caused by the presence of streaks of lymphoid tissue on the posterior pharynx. Tonsillar hypertrophy can also be seen. The neck should be examined for the presence of lymphadenopathy. The respiratory system must be examined for findings consistent with asthma. These include wheezing, tachypnea, and a prolonged expiratory phase of respiration.

CAUSES OF ALLERGIC RHINITIS

The causes of allergic rhinitis can differ depending on whether the symptoms are seasonal, perennial, or sporadic/episodic. Some patients are sensitive to multiple allergens and can have perennial allergic rhinitis with seasonal exacerbations. Although food allergy can cause rhinitis, particularly in children, it is rarely a cause of allergic rhinitis in the absence of gastrointestinal or skin symptoms. Seasonal allergic rhinitis is commonly caused by allergy to seasonal pollens and outdoor molds.

Pollens (Tree, Grass, and Weed)

Tree pollens, which vary by geographic location, are typically present in high counts during the spring, although some species produce their pollens in the fall. Grass pollens also vary by geographic location. Most of the common grass species are associated with allergic rhinitis. A number of these grasses are cross-reactive, meaning that they have similar antigenic structures (ie, proteins recognized by specific IgE in allergic sensitization). Consequently, a person who is allergic to one species is also likely to be sensitive to a number of other species. The grass pollens are most prominent from the late spring through the fall, but can be present year-round in warmer climates.

Weed pollens also vary geographically. Many weeds, such as short ragweed, a common cause of allergic rhinitis in much of the United States, are most prominent in the late summer and fall. Other weed pollens are present year-round, particularly in warmer climates.

Perennial allergic rhinitis is typically caused by allergens within the home, but can also be caused by outdoor allergens that are present year-round. In warmer climates, grass pollens can be present throughout the year. In some climates, individuals may be symptomatic because of trees and grasses in the warmer months and molds and weeds in the winter.

House Dust Mites

In the United States, two major house dust mite species are associated with allergic rhinitis. These mites feed on organic material in households, particularly the skin that is shed from humans and pets. They can be found in carpets, upholstered furniture, pillows, mattresses, comforters, and stuffed toys.

Animals

Allergy to indoor pets is a common cause of perennial allergic rhinitis. Cat and dog allergies are encountered most commonly in clinical practice. However, allergies have been reported to occur with most of the furry animals and birds that are kept as indoor pets. Although cockroach allergy is most frequently considered to be a cause of asthma, particularly in the inner city, it can also cause perennial allergic rhinitis in infested households. Rodent infestation may also be associated with allergic sensitization.

TREATMENT

The management of allergic rhinitis consists of three major categories of treatment: allergen avoidance, pharmacologic management, and immunotherapy. All aspects of treatment are more successful when exposure to allergens is decreased. Exposure to common allergens, such as dust mites, can be enhanced by methods such as removing the carpets from homes and encasing bedding in plastic.

Pharmacotherapy can involve the use of **antihistamines, decongestants, intranasal corticosteroids, and, in severe cases, systemic corticosteroids**. **Antihistamines** competitively antagonize the receptors for histamine, which is released from mast cells. This reduces the production of symptoms mediated by the release of histamine. "First-generation" antihistamines, including diphenhydramine, chlorpheniramine, and hydroxyzine, are inexpensive and available over-the-counter. Side effects include sedation and the anticholinergic effects of dry mouth, dry eyes, blurred vision, and urinary retention. Newer, so-called second-generation antihistamines, including loratadine, fexofenadine, and cetirizine, have much less penetration into the central nervous system, resulting in a lower incidence of sedation as a side effect. They also have fewer anticholinergic effects. They are, however, significantly more expensive than the older agents. Loratadine and cetirizine have recently become available without a prescription.

Decongestants, either given orally or intranasally, can be used to provide symptomatic relief of nasal congestion. These agents constrict blood vessels in the nasal mucosa and reduce the overall volume of the mucosa. The most commonly used agent is pseudoephedrine, an α-adrenoreceptor agonist. Oral decongestants can cause tachycardia, tremors, and insomnia. Rebound hyperemia and worsening of symptoms can occur with chronic use or upon discontinuation of nasal decongestants.

Corticosteroid nasal sprays are effective for the long-term management of allergic rhinitis. They reduce the production of inflammatory mediators and the recruitment of inflammatory cells. Systemic absorption of the steroid is relatively low, reducing the risk of complications associated with the chronic use of systemic corticosteroids. Side effects include nosebleeds, pharyngitis, and upper respiratory tract infections.

Leukotriene inhibitors are indicated both for allergic rhinitis and for maintenance therapy for persistent asthma. They are particularly useful in patients with both asthma and allergies or in those whose asthma may be triggered by allergens. Leukotriene inhibitors are taken orally and are only available by prescription.

Oral corticosteroids are potent inhibitors of cell-mediated immunity. The use of systemic steroids is limited by adverse effects, including suppression of the hypothalamic-pituitary-adrenal axis and hyperglycemia. Long-term use can lead to peptic ulcer formation, increased susceptibility to infection, poor wound healing, and the reduction of bone density. Because of these significant risks, systemic steroids are used only for severe allergies and are used in the lowest effective dose for the shortest possible time.

Desensitization therapy is frequently attempted in patients who remain symptomatic despite maximal medical therapy. The first step of this treatment is to test for specific antigens to which the person is allergic. The second step is to inject the patient with highly diluted concentrations of this antigen. The concentration of the antigen(s) in the injection is gradually increased, in an effort to reduce the patient's inflammatory response to the antigen(s). Injections are typically given weekly or biweekly. This process is expensive, time-consuming, and requires numerous injections. Patients and physicians must be prepared to address severe, even anaphylactic, reactions that may occur during the process.

ANAPHYLAXIS, URTICARIA, AND ANGIOEDEMA

Urticaria is characterized by large, irregularly shaped, pruritic, erythematous wheals. **Angioedema** is painless, deep, subcutaneous swelling that often involves the periorbital, circumoral, and facial regions. **Anaphylaxis** is a systemic reaction with cutaneous symptoms that is associated with dyspnea, visceral edema, and hypotension. The manifestations of anaphylaxis include hypotension or shock from widespread vasodilation, respiratory distress from bronchospasm or laryngeal edema, gastrointestinal and uterine muscle contraction, and urticaria and angioedema.

At the first suspicion of anaphylaxis, aqueous epinephrine 1:1000, in a dose of 0.2 to 0.5 mL (0.2-0.5 mg) is injected subcutaneously or intramuscularly. Repeated injections can be given every 15 to 30 minutes when necessary. Rapid intravenous infusion of large volumes of fluids (saline, lactated Ringer solution, plasma or plasma expanders) is essential to replace loss of intravascular plasma into tissues. Airway obstruction may be caused by edema of the larynx or by bronchospasm. Endotracheal intubation may be required. Bronchospasm responds to subcutaneous epinephrine or terbutaline. Antihistamines may be useful as adjuvant therapy for alleviating cutaneous manifestations of urticaria or angioedema and pruritus. All patients with anaphylaxis should be monitored for a period of time, for example, 24 hours.

ASTHMA

Asthma is a chronic disease characterized by airway hyperresponsiveness. There are recurrent muscle spasms of the bronchi and bronchioles. Essentials of diagnosis include recurrent wheezing, shortness of breath, or cough, an increase in airway secretions, and dyspnea. A history of allergies in children is also common.

Asthma results in mild to severe obstruction to airflow in the tracheobronchial tree. Viral infections and allergens are two of the major triggers in childhood asthma. A history of wheezing, shortness of breath, dyspnea, cough, increased sputum production, and chest tightness is often found. The physical examination may reveal wheezing, increased expiratory phase, tachypnea, cyanosis, tachycardia, or use of accessory respiratory muscles.

Asthma is classified as intermittent, mild persistent, moderate persistent or severe persistent, based on the frequency of symptoms and the amount of airway obstruction (Table 6–1). **Status asthmaticus** is an obstruction that lasts for days or weeks and is refractory to treatment.

Treatment involves the avoidance of triggers and the use of medications, both to reduce the frequency of exacerbation and to relieve the acute symptoms. These medications include β-adrenergic agonists, inhaled corticosteroids, leukotriene modifiers, mast cell stabilizers, and systemic corticosteroids.

The rapid acting β_2-adrenergic agonist albuterol is the mainstay treatment for acute symptomatic relief in asthma. It works to rapidly relax bronchial smooth muscle. It also reduces the release of mast cell mediators and increases mucociliary clearance. Long-acting β_2-adrenergic agonists have the same mechanism of action, but are not used for acute bronchospasm. They are effective at reducing the frequency of exacerbation in persistent asthma. The primary treatment of persistent asthma is the daily use of inhaled corticosteroids, which reduce the production of inflammatory mediators and reduce vascular permeability. They do not have an effect on smooth muscle relaxation and should not be used for an acute exacerbation. Leukotriene inhibitors, which

either reduce the production of these inflammatory mediators (zileuton) or competitively antagonize their receptors (zafirlukast, montelukast), are also effective in the prevention of exacerbation in persistent asthma. Systemic corticosteroids are used in the treatment of acute exacerbation and for prophylaxis in severe persistent asthma. Table 6–1 lists the specific indications for uses of each medication.

CONJUNCTIVITIS

Conjunctivitis is an infection of the palpebral and/or bulbar conjunctiva. It is the most common eye disease seen in community medicine. Most cases are caused by bacterial or viral infection. Other causes include allergy and chemical irritants. The mode of transmission of infectious conjunctivitis is usually direct contact to the opposite eye or to other persons via fingers, towels, or handkerchiefs.

The organisms isolated most commonly in bacterial conjunctivitis are *Staphylococcus*, *Streptococcus*, *Haemophilus*, *Moraxella*, and *Pseudomonas*. There is no blurring of vision and only mild discomfort. In severe cases, examination of stained conjunctival scrapings and cultures are recommended. The disease is usually self-limited, lasting about 10 to 14 days if untreated. A sulfonamide instilled locally three times daily will usually clear the infection in 2 to 3 days.

Epidemic keratoconjunctivitis (pink eye) is highly contagious and spread by person-to-person contact or fomites. The most common cause is adenovirus. It is usually associated with pharyngitis, fever, malaise, and preauricular lymphadenopathy. Locally, the palpebral conjunctiva is red with a copious watery discharge and scanty exudates. Local sulfonamide therapy might prevent secondary bacterial infection; hot compresses reduce the discomfort of the associated lid edema; weak topical steroids may be necessary to treat the corneal infiltrates. The disease usually lasts at least 2 weeks.

Noninfectious causes of conjunctivitis include allergic and chemical irritants. Symptoms of allergic conjunctivitis include itching, tearing, redness, stringy discharge, and sometimes photophobia. Treatment can include the use of oral antihistamines or topical antihistamine or anti-inflammatory eye drops.

Table 6–1 CLASSIFICATION OF ASTHMA SEVERITY

CLASSIFICATION	DAYS WITH SYMPTOMS	NIGHTS WITH SYMPTOMS	PEF OR FEV_1 (PEF IS % OF PERSONAL BEST; FEV_1 IS % OF PREDICTED)	TREATMENT*
Severe persistent	Continual	Frequent	≤60%	Preferred: high-dose inhaled steroid and long-acting long-acting β-agonist and consider omalizumab in patients with allergies If needed, high-dose inhaled steroid, long-acting β-agonist, and oral steroid and consider omalizumab in patients with allergies
Moderate persistent	Daily	>1 × /wk but not nightly	>60%-<80%	Preferred: low-dose inhaled steroid and long-acting β-agonist or medium-dose inhaled steroid Alternative: low-dose inhaled steroid and leukotriene modifier, theophylline, or zileuton If needed (particularly in patients with recurring severe exacerbations): Preferred: increase inhaled steroid within medium-dose range and long-acting β-agonist Alternative: increase inhaled steroid within medium-dose range and add leukotriene modifier, theophylline, or zileuton

Mild persistent	>2 d/wk but not daily	3-4/mo	≥80%	Preferred: low-dose inhaled steroid Alternative: cromolyn, nedocromil, leukotriene modifier or theophylline
Intermittent	≤2/wk	≤2/mo	≥80%	No daily medication needed Severe exacerbations may occur, separated by long periods of normal function and no symptoms, a course of systemic corticosteroids is recommended

*__All patients: short-acting bronchodilator as needed for symptoms__. *Data from National Institutes of Health.* Practical Guidelines for the Diagnosis and Management of Asthma. *Washington, DC: National Institutes of Health, National Heart, Lung and Blood Institute; 1997; and the National Asthma Education and Prevention Program (NAEPP) Expert Panel Report.* Guidelines for the Diagnosis and Management of Asthma—Update on Selected Topics, 2002. *Washington, DC: National Institutes of Health, National Heart, Lung and Blood Institute; 2007.*

Comprehension Questions

6.1 A 30-year-old man has both mild persistent asthma and chronic environmental allergies. Which of the following medications is indicated for the management of this patient's conditions?

A. Inhaled albuterol (short-acting β-adrenergic agonist)
B. Intranasal fluticasone (corticosteroid)
C. Oral montelukast (leukotriene modifier)
D. Oral cetirizine (second-generation antihistamine)

6.2 An 18-year-old adolescent male presents for follow-up of his asthma. He has symptoms no more than 1 day per week and 1 night per month. Which of the following is the most appropriate treatment for him?

A. Daily inhaled mometasone (inhaled corticosteroid)
B. As-needed use of inhaled albuterol
C. Daily use of salmeterol (a long-acting β-adrenergic agonist)
D. Daily use of zafirlukast (a leukotriene modifier)

6.3 A 56-year-old man presents to his physician with symptoms consistent with allergic rhinitis. His past medical history is positive for benign prostatic hyperplasia. He continues to work in a warehouse as a forklift operator. Which of the following medications should be used to treat this patient?

A. Diphenhydramine
B. Hydroxyzine
C. Chlorpheniramine
D. Fexofenadine

ANSWERS

6.1 **C.** Montelukast is indicated for both the management of persistent asthma and chronic allergies. Nasal steroids and oral antihistamines are indicated only for allergies.

6.2 **B.** This patient has mild intermittent asthma, as he has symptoms less than twice per week and less than 2 nights per month. The recommended treatment for mild intermittent asthma is the as-needed use of a short-acting inhaled β-agonist.

6.3 **D.** The second-generation antihistamines, such as fexofenadine, are less sedating and have fewer anticholinergic side effects than the first-generation antihistamines. They would be a better choice for someone who operates heavy machinery and has benign prostatic hyperplasia. However, they are no more effective at symptom relief than the first-generation anti-histamines listed above.

Clinical Pearls

- The management of allergic rhinitis consists of three major categories of treatment: allergen avoidance, pharmacological management, and immunotherapy.
- For the diagnosis of asthma look for recurrent wheezing, cough, increase in airway secretion, or dyspnea.
- At the first suspicion of anaphylaxis, aqueous epinephrine 1:1000 in a dose of 0.2 to 0.5 mL (0.2-0.5 mg) is injected subcutaneously or intramuscularly. The airway should always be assessed and patient intubated if necessary to secure breathing.

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Case 7

A 55-year-old man comes into your office for follow-up of a chronic cough. He also complains of shortness of breath with activity. He reports that this has been getting worse over time. As you are interviewing the patient, you note that he smells of cigarette smoke. Upon further questioning, he reports smoking 1 pack of cigarettes per day for the past 35 years and denies ever being advised to quit. On examination, he is in no respiratory distress at rest, his vital signs are normal, and he has no obvious signs of cyanosis. His pulmonary examination is notable for reduced air movement and faint expiratory wheezing on auscultation.

- What would you recommend to this patient?
- What interventions are available to aid with smoking cessation?

ANSWERS TO CASE 7:
Tobacco Use

Summary: A 55-year-old man with a 35 pack/year history of smoking presents with a chronic cough and progressively worsening dyspnea.

- **Recommendations to this patient:** This patient should be advised to quit smoking; one strategy, using the 5 As, is discussed below.
- **Interventions available to help with smoking cessation:** Counseling to quit smoking along with pharmacologic assistance with bupropion, varenicline, or nicotine replacement.

ANALYSIS

Objectives

1. Know the many medical conditions and complications related to tobacco use.
2. Develop a framework for the discussion of tobacco use and promotion of smoking cessation.
3. Know the currently available pharmacologic agents that are used to aide in smoking cessation.

Considerations

This is a 55-year-old man with a long smoking history who presents with a chronic cough and worsening dyspnea. The most important first steps are to address the airway and breathing, and ensure that there is not a respiratory emergency. Assessment of the patient's air movement, oxygenation, and degree of respiratory distress are important. After evaluating his condition and ascertaining whether it is chronic lung disease or an exacerbation such as bronchitis superimposed on chronic obstructive pulmonary disease (COPD), therapy may be enacted. Bronchodilator therapy, antibiotic therapy depending on the character of the sputum and the chest radiograph findings are typically used. One critical component to therapy includes smoking cessation. Physician intervention is paramount, and the use of adjuvant therapies helps to increase the success.

APPROACH TO
Tobacco Cessation

DEFINITIONS

PREGNANCY CATEGORY B: FDA category for use of a medication in pregnancy in which animal studies have shown no harm to a fetus but human studies are not available OR animal studies have shown harm to a fetus but studies in pregnant women have not shown harm.

PREGNANCY CATEGORY C: Animal studies have shown adverse fetal effects and there are no adequate studies in humans OR no animal studies have been conducted and there are not adequate studies in humans.

PREGNANCY CATEGORY D: Human studies have shown potential adverse fetal effects however the benefits of therapy may outweigh the potential risks.

CLINICAL APPROACH

Tobacco use is the single greatest cause of preventable death. It is responsible for increased death rates from cancer, cardiac, cerebrovascular, and chronic pulmonary disease. Approximately 20% of the adult population reported smoking in 2004 and over 400,000 deaths per year are a result of tobacco use. Smoking also affects the health of those in close contact with people who smoke. Each year, 38,000 deaths from cancer and heart disease in nonsmokers are attributable to secondhand smoke. Smoking in pregnancy is associated with prematurity, intrauterine growth restriction, stillbirth, spontaneous abortion, and infant death. Smoking cessation reduces all of these risks. However, despite this evidence, it is difficult for smokers to quit. Health care providers are important in the effort to reduce tobacco use and its related disease burden.

Research indicates that physician intervention, even in brief encounters, increases tobacco cessation rate. Furthermore, cessation rates increase with increased physician time and frequency of encounters to address tobacco use, but the optimal duration and frequency has not been defined. **The process of discussing tobacco use and cessation involves several steps; one useful framework is the "five As":**

- **Ask** about tobacco use: ask the patient at each visit about current tobacco use;
- **Advise** to quit through clear personalized messages: let the patient know of his/her specific risks of tobacco use; in the sample case, talk to the patient about how the persistent cough and dyspnea can be related to the tobacco use and how cessation might be helpful;
- **Assess** willingness to quit: find out the patient's thoughts about quitting and if the patient is ready to proceed;

- **Assist** to quit: including counseling and pharmacologic treatment;
- **Arrange** follow-up and support.

Multiple factors may be part of a patient's unwillingness to quit. **A strategy to enhance motivation** includes discussing the specific **relevance** to the patient of smoking cessation, **risks** of ongoing tobacco use, **rewards** to quitting (financial, health, social), **roadblocks** to quitting (withdrawal, discouragement because of failed past attempts, enjoyment of smoking), and **repetition** (readdressing the problem at each visit and reminding patients most people attempt to quit several times before being successful).

In pregnancy, it has been found to be helpful to discuss specific risks to the mother and fetus of continued tobacco use. While cessation prior to pregnancy is ideal, cessation at any time during pregnancy is associated with health benefits for patient and fetus, so ongoing discussions are encouraged. The pregnant patient will also need ongoing support after delivery to reduce the risk of remission after delivery.

Pharmacologic Therapy

In addition to counseling and reviewing the risks and benefits of quitting, the use of pharmacologic aids can increase the likelihood of successful smoking cessation when a patient has decided to quit. There are two broad modalities approved by the FDA to assist with smoking cessation: nicotine replacement and nonnicotine medications. Nictotine replacement products include gum, patch, inhaler, nasal spray, and lozenge. The approved nonnicotine medications are bupropion sustained release (brand name: Zyban) and varenicline (brand name: Chantix).

Bupropion was the first nonnicotine treatment for smoking cessation approved by the FDA. It is thought to work by blocking uptake of norepinephrine and/or dopamine. It is contraindicated in patients with eating disorders, monoamine oxidase (MAO) inhibitor use in the last 2 weeks, or a history of seizure disorder. The medication should be started 1 to 2 weeks before the quit date and the usual dose is 150 mg a day for 3 days then 150 mg twice a day. The usual course of treatment is 7 to 12 weeks, but it can be used for up to 6 months as maintenance therapy. This treatment can be used alone or in combination with nicotine-based treatments. In two studies comparing bupropion sustained release to placebo, the cessation rate for the bupropion group was 30%, compared to 17% in the placebo group.

Varenicline is the newest agent approved for assistance with smoking cessation. It is a nicotinic receptor partial agonist that may reduce cravings for nicotine, reduce nicotine withdrawal symptoms, and block some of the binding of nicotine from cigarettes. Its efficacy at assisting with smoking cessation is similar to that of bupropion. It has not been studied for use with nicotine supplementation or with bupropion. Varenicline has been associated with neuropsychiatric symptoms, including changes in behavior, agitation, depression,

and suicidal behaviors. It should be used with caution in anyone with a history of psychiatric disorders and all persons using the medication should be monitored closely for these behaviors.

Nicotine replacement therapies as a group increase smoking cessation rates over placebo. They can be used in combination therapy, which may increase cessation rates over monotherapy.

Nicotine gum is available in 2 mg and 4 mg of nicotine per piece. The patient chews a piece of the gum until the patient feels a peppery taste in the mouth, "parks" the gum in a cheek until the sensation goes away, and then chews the gum again until the peppery sensation returns. The 4-mg dose is recommended for those who smoke more than 25 cigarettes per day and the 2-mg dose for those who smoke fewer than 25 cigarettes per day. Common pitfalls include not "parking" the gum (ie, chewing constantly) and not using enough pieces per day initially. Consider advising the patient to use the gum on a scheduled basis, rather than as needed, initially, and then slowly tapering the number of pieces per day.

The nicotine cartridge inhaler is available by prescription and has also been found to be effective in increasing smoking cessation rates. Each cartridge contains 4 mg of nicotine in 80 inhalations. The recommended dose is 6 to 16 cartridges per day. The inhaler can be used over several months, with a gradual tapering of the dose. For both the gum and inhaler, acidic beverages can reduce absorption of the nicotine from the buccal mucosa, so the patient should avoid ingestion within 15 minutes of use of these products.

Another therapeutic option is the nicotine nasal inhaler. The inhaler provides 0.5 mg of nicotine per inhalation and can be used at a starting rate of 1 to 2 doses per hour, for a maximum of 40 doses per day (5 doses per hour). The inhaler can also be used over months, with gradual tapering of the dose. Nasal irritation is the most common side effect.

The nicotine patch is a passive nicotine replacement system, compared to the other methods outlined above. There are two common over-the-counter forms of the nicotine patch: Nicoderm CQ, which comes in multiple doses (21, 14, and 7 mg of nicotine per patch) and are meant to be worn for 24 hours a day, and Nicotrol, which has 15 mg of nicotine and is meant to be worn for 16 hours a day. The patch is replaced daily, and consideration should be given to starting with higher-dose patches in heavy smokers. Treatment with the patch for less than 8 weeks is as effective as longer treatment periods. The most common side effect is irritation of the skin at the site of the patch.

The nicotine inhaler, nasal spray, and gum are pregnancy category D drugs; the patch is pregnancy category C, and bupropion is pregnancy category C. These products can be considered for use in the pregnant smoker if counseling is insufficient to promote cessation, and if, in discussion with the patient, it is determined that the risks of continued smoking outweigh the risks of the medication. Varenicline is pregnancy category C. It has not been studied in pregnancy and should only be used if the benefit justifies the potential risk to the fetus.

The United States Preventive Services Task Force (USPSTF) strongly recommends screening all adults and pregnant patients for tobacco use and offering cessation intervention for those who use tobacco products (Level A recommendation). At this time there is insufficient evidence to recommend for or against screening children and adolescents for tobacco use or offering interventions to prevent tobacco use or promote cessation (Level I recommendation). However, as most smokers start in this age group, the USPSTF notes that providers may use individual discretion when discussing tobacco use in this population.

Comprehension Questions

7.1 A pregnant woman who smokes 1 pack of cigarettes a day asks for your advice regarding smoking cessation while she is pregnant. Which of the following statements is most appropriate?

A. Bupropion is pregnancy category C and relatively safe in pregnancy.
B. Varenicline is pregnancy category B and relatively safe in pregnancy.
C. Nicotine gum delivers a lower, safer dose of nicotine than the nasal spray.
D. The use of smoking cessation products during pregnancy frequently leads to adverse outcomes.

7.2 Which of the following statements regarding available treatments for smoking cessation is accurate?

A. Bupropion can be used in combination with nicotine supplements.
B. Nicotine gum is most effective if chewed continuously, to promote a constant release of the nicotine.
C. Nicotine supplements are most effective when used as needed for withdrawal symptoms.
D. All of the available agents are more effective when used in combinations with each other.

7.3 Which of the following counseling strategies is most likely to enhance your patients' smoking cessation rates?

A. Discuss smoking cessation techniques only with patients who ask for your advice, as others will resent your suggestions.
B. Emphasize primarily the health risks of smoking.
C. Note in each patient's chart that you have discussed cessation, so that you don't repeat the message to the same patient at subsequent visits.
D. Ask about smoking cessation at each encounter.

ANSWERS

7.1 **A.** Bupropion and Varenicline are both pregnancy category C. However, pharmacologic aids to increase the rate of smoking cessation during pregnancy can be used, after discussion with the patient of the risks and benefits of the medications and of continued smoking. Cessation of smoking at any time during the pregnancy is likely to provide health benefits for the mother and fetus. Nicotine gum delivers a higher does of nicotine than its nasal spray counterpart.

7.2 **A.** Bupropion can be used in combination with any of the nicotine supplementation products. The nicotine products can also be used in combination with each other. Varenicline has not been studied for use with other smoking cessation agents. Two common pitfalls in using nicotine supplementation are using supplementation only when having withdrawal symptoms and failing to use nicotine gum correctly. The gum should be chewed briefly and then parked in the cheek. It is less effective if chewed continuously.

7.3 **D.** Asking patients about tobacco use is a key to promoting cessation. It is important to ask each patient at each visit and to be prepared to provide advice and assistance at any time.

Clinical Pearls

- Most smokers require multiple attempts before successfully quitting for good. Remind your patients of this if they become discouraged in their efforts.
- Use the five As—Ask, Advise, Assess, Assist, and Arrange follow-up—to help your patients quit smoking.

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Case 8

A 16-year-old adolescent female presents to your office with the complaint of greenish vaginal discharge for the past 2 months and the recent onset of lower abdominal pain. She reports that her last period was about $2^1/_2$ months ago. She is sexually active with two partners and has never used a condom or any other contraception with either. On physical examination she is not febrile with normal blood pressure and pulse. She has greenish discharge from the cervix with friability and cervicitis. There is no cervical motion tenderness. Her urine pregnancy test is positive. A cervical sample is positive for *Chlamydia* and negative for *N. gonorrhea*. Her rapid plasma reagin (RPR) is nonreactive and an HIV test is negative. The patient is treated with appropriate antibiotics and counseled concerning safer sex practices. You also inform the patient regarding her risk for HIV conversion, even though today's test was negative. The patient asks if you are going to tell her mother that she is pregnant and has this infection. You inform the patient that because of patient confidentiality and ethical considerations you will not disclose this information to her mother without her consent. She tells you that she does not want her mother to know and she does not want her boyfriends to know she is infected.

- What should you do?
- What should you tell the patient?
- What are the ethical considerations?
- What are the guidelines for reporting communicable diseases?

ANSWERS TO CASE 8:
Medical Ethics

Summary: The patient is a teen who is pregnant and has a sexually transmitted infection. She engages in high-risk sexual behavior.

- **What you should do and what you should tell the patient:** You must inform the patient that you have to contact the state health department. The department will contact her and will contact her partners without disclosing her identity. You might also advise the patient to cooperate fully with the health department to avoid phone calls or letters received at home. It is also important to stress to the patient the importance of protecting her partners as well as herself, and that by disclosing to her partners, she may avoid further exposure.
- **Ethical considerations include:** Teenage pregnancy, confidentiality, sexually transmitted infection reporting, and emancipation.
- **Guidelines for reporting communicable diseases:** The guidelines for reporting communicable disease vary slightly from state to state. However, there is usually a formal mechanism for reporting to the state department of health. The physician may do it himself/herself or may elect to use an agent, such as a nurse or other medical facility staff member. It is a federal mandate to report communicable diseases; failure to do so may result in adverse legal, civil, and even criminal actions. In the state of Texas, failure to report communicable diseases is considered a class B misdemeanor.

ANALYSIS

Objectives

1. Discuss confidentiality and its ethical and legal considerations when treating adolescent or pregnant adolescent patients.
2. Understand the legal obligations for reporting communicable diseases and informing partners.

Considerations

There are several considerations involved in this case. The first issue is pregnancy. In some states, the patient would be considered emancipated. Consequently, legally she can make decisions regarding her pregnancy-related health care (excluding abortion) without notice to or the express consent of her parents. In addition, she has a sexually transmitted infection, which is a reportable condition; thus the physician or the physician's agent **must** report this to the

state health department for surveillance and infection control. She is also very concerned about informing her partners about the infection. There are also issues of confidentiality.

APPROACH TO
Medical Ethics

DEFINITIONS

EMANCIPATION: Emancipation is a legal process in which a person who is younger than the age of 18 years petitions the court to have herself/himself declared a legal adult. Laws for emancipation vary by state. Emancipation ends the parents' legal duty to support the minor, and also ends the parents' right to make decisions about the minor's residence, education, health care, and to control the minor's conduct. However, this does not include the ability to consume alcohol, use tobacco, or exercise voting rights.

MATURE MINOR DOCTRINE/RULE (JUDICIAL BYPASS): The mature minor exception to the need for parental consent for medical care is based on the West Virginia Supreme Court case *Belcher v.* CAMC. Statute and court decisions in many states may vary. A minor may consent to receive medical care without the consent of the parents or guardian if deemed "mature" by the judicial system.

CLINICAL APPROACH

According to the Society for Adolescent Medicine, "the overall goal in clinical practice is to deliver appropriate high quality healthcare to adolescent patients, while encouraging communication between parents or other trusted adults without betraying the adolescent's trust in the healthcare professional." It is very important to gain the confidence of adolescent patients because if the patient does not believe that the health-care provider will keep the patient's health information confidential, the patient is less likely to seek health care when needed. Confidential health care should be provided for all adolescent patients; however, the physician must consider some very important issues, including: Is the teen self-supporting? Is the minor mature enough to make his or her own medical care decisions? Would disclosure without consent harm the patient?

Ethics

Ethical considerations when treating adolescent patients can be complex and one should use the **moral principles of ethics,** which include **autonomy, beneficence,**

nonmaleficence, and justice to guide clinical decisions to maintain confidentiality. Respect for **autonomy** should involve respect for the patient's wishes, choices, and beliefs when deciding what is best for the patient. It is important to understand the dynamics of the parent-child relationship and why the teen does not want to disclose important medical information to parents. This type of dialogue may reveal very important things about the child's current situation and help to guide your decision making. Knowing the intricacies of the family dynamic may also help the clinician and the patient develop solutions to aid in disclosure of very important health-related issues.

Nonmaleficence implies that the physician will do nothing to harm the patient, which includes emotional and psychological harm. Failure to maintain confidentiality may result in some emotional distress for the patient. Moreover, the physician should not apply the same moral standards to every patient. Some teens are more mature than others and the physician should use his or her judgment with each adolescent patient.

In addition, the treating physician should apply the principle of **beneficence,** which requires action to further a patient's welfare. In other words, do the right thing for the patient. Maintaining confidentiality may aid in full disclosure of symptoms, life situations, and so on. Full disclosure of pertinent medial information can help the physician provide the most comprehensive care to the patient.

Justice implies the fair and nonbiased treatment of the patient regardless of age, sex, or ethnicity. Consequently, adolescent patients should be given the same level of care as adults, without having the fear of disclosure, when they are mentally capable of receiving care.

In most cases, every attempt should be provided to ensure confidentiality. However, **there are instances when it would be in the best interest of the patient to disclose medical information.** Examples of these situations could include patients with homicidal or suicidal ideation or serious chemical dependence, and in suspected cases of abuse. Disclosure of medical information should only be considered when the life of the adolescent must be protected. It is also important to point out that, in most cases, adolescents are not responsible for payment of medical services. The parent or the guardian usually has to assume the responsibility for payment. Thus, the maintenance of confidentiality in these cases is an issue. Because there are no clear-cut guidelines in this situation, it is important to encourage open dialogue between the patient and the patient's parent. However, in instances when this is not possible the physician must use his or her own clinical judgment while considering ethical issues and must act in the best interest of the patient.

Legal Considerations

There are laws in place to protect the confidentiality of health-care information. In general, the law requires the consent of the parent when health-care is provided to minors; there are, however, exceptions, such as emergencies,

care for the **"mature minor,"** and when the minor is legally entitled to consent to their own medical treatment.

Laws that allow minors to consent to medical treatment vary from state to state. In some states minors are allowed to consent to medical therapy based on status, such as emancipation, marriage, pregnancy, living apart from parents, and when given the status of "mature minor." The mature minor rule was created in 1967 and is based on the West Virginia Supreme Court case *Belcher v. CAMC*, which allowed health-care providers to treat a youth as an adult based on an assessment and documentation of the adolescent's maturity level. According to this decision, a court must determine that a minor is deemed mature, which determination is based on various factors, including age; ability; experience; education and/or training; degree of maturity and/or judgment exhibited; conduct and demeanor; and capacity to understand the risk and benefits of medical treatment. The process to become a mature minor is known as judicial bypass and may vary from state to state. This exception to parental consent must be received from a court.

In addition, **adolescents may consent to medical care if they are considered emancipated**. Emancipation implies that a minor must be of a certain age (which varies by state), must live apart from his or her parents, and must be self-sufficient. Minors are also considered emancipated if they are self-supporting, not living at home, married, pregnant or a parent, in the military, or declared emancipated by the judicial system.

In some states, **consent to health care may be based on the type of care the adolescent is seeking.** Examples of the types of health-care services that may be obtained without parental consent may include maternity services; contraceptive management; treatment and diagnosis of sexually transmitted infections (including HIV) or other reportable diseases; treatment of drug or alcohol problems; and care related to sexual assault or mental health services. These provisions are very important because they allow the necessary assessment and treatment of important health-related issues. Moreover, research shows that adolescents are more likely to seek medical care if confidentiality is protected.

Reportable Diseases

Reporting sexually transmitted infections (STIs), HIV, and other reportable illnesses can be stressful for the patient. This may be particularly stressful for the adolescent. The **information may be reported by the physician or by the physician's designated appointee.** All those involved in the oversight of blood products, including clinical laboratories or blood banks, are also required to report STIs and other reportable conditions to the state's health department. It is state and federal law that these illnesses be reported in a timely fashion to the state health department.

In addition, it is **mandatory that the information be disclosed to partners.** Partner reporting is a way to control the spread of disease and to ensure

prompt and proper diagnosis and treatment of all those who may be affected. Partner notification can occur in either of two ways: by patient referral or by the department of health staff. The patient can contact his/her partner(s) for referral, diagnosis, and treatment. Alternatively, the partner(s) may be notified and counseled by department of health staff, if the patient is unwilling to inform them. In the setting where a patient is unwilling to inform his/her partner(s) of a reportable illness that places the partner(s) at risk, the healthcare provider has a legal and ethical obligation to inform the partner(s) (if known by the provider) that they are at risk.

Teenage Pregnancy and Confidentiality

Issues regarding teenage pregnancy and consent to disclose information regarding pregnancy are quite controversial. Laws for reporting vary by state and the specifics may become quite daunting. For the purposes of this case, focus is limited to generalities. One must understand the laws pertaining to this issue in the state in which he or she practices. In the state of Texas, as may be the case in other states, a clinician is not required to inform the parents of issues related to the pregnancy of a minor without the child's consent, but it is not mandatory for the adolescent to give consent for a physician to disclose information related to pregnancy to parents. However, studies demonstrate that failure to maintain confidentiality in "sensitive" health-related issues may inhibit appropriate health care delivery to the adolescent.

In Texas, the law does not allow state funds to be used for contraception without the consent of the parent. Moreover, in most states, an adolescent younger than age 18 years cannot give consent to abortion services without the consent of one or both parents. This issue has been the subject of political debate for many years. Proponents of mandatory consent laws believe that it is in the best interest of the minor for her parent(s) or guardian to be informed of her pregnancy and decision to obtain abortion services, stating that by doing so, communication among adult and child may be improved.

Opponents of these laws, however, see them as a threat to the well-being of young women by forcing them to seek abortion services from unlicensed facilities, crossing state lines to obtain abortions, and increasing medical risk. The risk to young women may be increased by enforcing mandatory wait periods, which could mean having abortions later in the pregnancy than desired.

Currently, only six states do not require consent from parents to obtain abortion services. In a state in which consent is required, there are some legal alternatives for young women. For example, if an adolescent is considered emancipated, then consent from parents or guardians is not required. Waivers of consent (judicial bypass) may also be obtained through the judicial system.

Conclusion

Pregnancy-related care, abortion services, and reportable illnesses are complex and a clinician should seek legal advice when appropriate. However, in

general, it is preferable to protect the confidentiality of the minor unless it is unreasonable or unsafe to do so. It is also important to educate teens and parents of the importance of open communication and issues related to confidentiality in medical care.

Comprehension Questions

8.1 A 14-year-old adolescent female is here to see you for complaints of greenish vaginal discharge. She is sexually active with one partner and does not use condoms. You do a culture and find that she has *Trichomonas* vaginitis. She asks you not to tell her mother about this diagnosis or that she is sexually active. Which of the following statements is most accurate regarding disclosure or nondisclosure of this information to her parents?

A. You can keep this information confidential. However, it is advisable to talk with the teen about her sexual history and discuss communication issues between her and her parents.
B. Since she is a minor, you must disclose this information to her parents.
C. You can only keep this confidential for today for enhancing therapy, but then disclosure to the parents must be demonstrated and documented.
D. You may keep this confidential from the parents but you must call the partner to notify him of the infection.

8.2 In which of the following situations may a physician keep information confidential from parents or other authorities?

A. The physician finds injuries consistent with physical abuse while examining a 13-year-old but the patient fears further injury if the abuse is reported.
B. A depressed teenager reports a strong desire to kill herself and that she has secretly obtained a gun that she keeps in her bedroom.
C. An undocumented immigrant patient has active tuberculosis and fears deportation if the illness is reported.
D. A 19-year-old female college student, who is still on her parents' insurance plan, reports a consensual sexual relationship with a 35-year-old man and requests contraception but does not want her parents to know.

8.3 Which of the following is most accurate regarding the term "emancipation" as it applies to a minor?

A. Able to vote
B. Able to purchase and consume alcohol
C. Able to make their own medical decisions without parental consent
D. Legally financially independent

8.4 Which of the following statements regarding a minor's ability to consent for an abortion is most accurate?

A. Because of medical confidentiality, a minor is able to consent to any medical therapy she chooses without the consent of her parents or guardian.
B. Although consent requirements for abortion services vary depending on the state, most states either have some form of required consent for abortion services to minors or a mandatory wait period.
C. There are no states in which a minor can obtain an abortion without the consent of a parent or guardian.
D. A minor cannot consent to any medical therapy without her parents' approval unless she has received a court order.

ANSWERS

8.1 **A.** The law does not require the disclosure of sensitive medical information to parents. However, in some states it is not forbidden to disclose that information. A clinician must use his or her best judgment when deciding whether to disclose medical information. More importantly, the physician should recognize the importance of confidentiality when treating patients and encourage open communication between adolescents and parents when it is reasonable to do so. Partner notification can occur by patient referral or by health department staff.

8.2 **D.** All states have laws mandating the reporting of certain conditions, even if the patient objects. The specific conditions may vary from state to state, so the physician must be aware of the rules where he/she practices. Child abuse must be reported to appropriate authorities if suspected in all states. Similarly, certain infections, such as active tuberculosis, must be reported to public health officials. Active suicidal ideation, especially if there is a plan and access to agents necessary to implement the plan, may lead the physician to intervene to prevent the action. Of the scenarios listed, only D does not obligate the physician to act.

8.3 **C.** Emancipation implies that the patient is able to make decisions regarding health-related issues but does not give the patient the right to vote, consume alcohol, or use tobacco products if the patient is not of legal age.

8.4 **B.** The laws regarding the consent for abortion services vary from state to state. Only six states currently allow a minor to have an abortion without the consent of or notification to parents.

Clinical Pearls

- Adolescent health care is a complex issue. However, the clinician should attempt to administer confidential health care to minors seeking care for sensitive medical issues when it is safe and appropriate to do so.
- It is very important for clinicians to know the laws regarding consent and confidentiality when treating adolescent patients of the states in which they practice.

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Case 9

A 65-year-old African-American woman presented to the emergency room complaining of worsening shortness of breath and palpitations for about 1 week. She reports feeling "dizzy" on and off for the past year; the dizziness is associated with weakness that has been worsening for the past month. She has been feeling "too tired" to even walk to her backyard and water her flower bed that she used to do "all the time." She has been so dyspneic walking up the stairs at her home that she moved downstairs to the guest room about a week ago. Review of systems is significant for knee pain, for which she frequently takes aspirin or ibuprofen; otherwise the review of systems is negative. She has no significant medical history and has not been to a doctor in several years. She had a normal well-woman examination and screening colonoscopy about 5 years ago. She occasionally has an alcoholic drink and denies tobacco or drug use. She is married and is a retired shopkeeper. On examination, her blood pressure is 150/85 mm Hg; her pulse is 98 beats/min; her respiratory rate is 20 breaths/min; her temperature is 98.7°F (37.1°C); and her oxygen saturation is 99% on room air. Significant findings on examination include conjunctival pallor, mild tenderness with deep palpation in the epigastric and left upper quadrant (LUQ) region of the abdomen with normal bowel sounds, and no organomegaly but a positive stool guaiac test. The remainder of the examination, including respiratory, cardiovascular, and nervous systems, was normal.

- What is the most likely diagnosis?
- What is your next diagnostic step?
- What is the next step in therapy?

ANSWERS TO CASE 9:
Geriatric Anemia

Summary: A 65-year-old woman with worsening dyspnea on exertion, fatigue, dizziness, and palpitations. She is found to have conjunctival pallor and guaiac-positive stool.

- **Most likely diagnosis:** Anemia secondary to gastrointestinal bleeding; other considerations should include new-onset angina, congestive heart failure, and atrial fibrillation.
- **Next diagnostic step:** A complete blood count (CBC) to evaluate for the anemia. To evaluate for the other conditions on your differential diagnosis list, you should perform an electrocardiogram (ECG) and cardiac enzymes. A prothrombin time (PT) and partial thromboplastin time (PTT) to look for coagulation abnormalities would be helpful as well.
- **Next step in therapy:** Admission as an inpatient for further workup, including blood transfusion (if needed), completion of two more sets of cardiac enzymes, and ECGs. A gastroenterology consult for esophagogastroduodenoscopy (EGD) and colonoscopy is appropriate because of the positive guaiac findings.

ANALYSIS

Objectives

1. Know a diagnostic approach to anemia in geriatrics.
2. Be familiar with a rational workup for anemia of different origins.

Considerations

A 65-year-old woman who has developed worsening dyspnea and palpitations over 1-week period of time needs to be evaluated for cardiac and respiratory problems despite the gradual onset of symptoms. Specifically, in a postmenopausal woman, signs and symptoms of angina or acute myocardial infarction may not always have a typical presentation. That the patient has been feeling weak and has conjunctival pallor warrants testing for anemia. As evaluation with serial cardiac enzymes and ECGs is part of the workup, admission into the hospital is appropriate.

Assuming that the initial workup for cardiac and pulmonary causes is negative and that the hemoglobin and hematocrit levels are low, a thorough evaluation for the cause of the anemia is necessary. A CBC with peripheral smear, reticulocyte count, iron study, vitamin B_{12} and folic acid levels would provide

clues to the type of anemia that this patient has. A gastroenterology consult for possible EGD and colonoscopy to further investigate the source of gastrointestinal bleeding should be considered. The presence of epigastric and LUQ pain, along with long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs), should also raise a flag for testing to rule out a bleeding ulcer.

The presence of other findings may direct your workup toward other diagnoses. If this patient were from a developing country, the possibility of intestinal parasites would need to be considered. If the PT and PTT were abnormal, GI bleeding from a coagulopathy or liver disease would be possibilities. Weight loss, lymphadenopathy, and coagulopathy may warrant evaluation for nongastrointestinal malignancies, such as leukemias or lymphomas. In younger patients, sickle cell disease, thalassemias, glucose-6-phosphate dehydrogenase (G6PD) deficiency, and other inherited causes of anemia would be on the differential diagnosis list. These are unlikely to manifest as an initial diagnosis at the age of 65 years.

APPROACH TO
Anemia in Geriatric Population

DEFINITIONS

ANEMIA: According to the World Health Organization (WHO), a hemoglobin level of less than 12 g/dL in women and less than 13 g/dL in men.

NHANES: The National Health and Nutrition Examination Surveys.

CLINICAL APPROACH

Epidemiology

The prevalence of anemia in Americans older than age 65 years is estimated at 9% to 45%. There is **a wide variation in the rates of anemia in different ethnic and racial groups,** with NHANES data showing the highest rates in non-Hispanic blacks and lowest rates in non-Hispanic whites. These differences are reportedly a result of biologic, not socioeconomic, differences. Most studies show the rate of anemia to be higher in men than women.

Clinical Presentation

Fatigue, weakness, and dyspnea are symptoms that are commonly reported by elderly persons with anemia. These vague and nonspecific symptoms are often ignored by both patients and physicians as symptoms of "old age." Anemia may result in worsening of symptoms of other underlying conditions. For

example, the reduced oxygen-carrying capacity of the blood as a consequence of anemia may exacerbate dyspnea associated with congestive heart failure.

Certain signs found on examination may prompt a workup for anemia. **Conjunctival pallor is recommended as a reliable sign of anemia in the elderly.** Other signs may suggest a specific cause of anemia. Glossitis, decreased vibratory and positional senses, ataxia, paresthesia, confusion, dementia, and pearly gray hair at an early age are signs suggestive of vitamin B_{12}-deficiency anemia. Folate deficiency can cause similar signs, except for the neurologic deficits. Profound iron deficiency may produce koilonychias. Other clinical manifestations of anemia include jaundice and splenomegaly. Jaundice can be a clue that hemolysis is a contributing factor to the anemia, while splenomegaly can indicate that a thalassemia or neoplasm may be present.

Initial workup of anemia should include a CBC with measurement of red blood cell (RBC) indices, a peripheral blood smear, and a reticulocyte count. Further laboratory studies would be indicated based on the results of the initial tests and the presence of symptoms or signs suggestive of other diseases.

The most common cause of anemia with a low mean corpuscular volume (MCV), microcytic anemia, is iron deficiency. Iron deficiency could be confirmed by subsequent testing that shows a low serum iron, low ferritin, and high total iron-binding capacity (TIBC). Other causes of microcytic anemia include thalassemias and anemia of chronic disease. In the elderly, iron deficiency is frequently caused by chronic gastrointestinal blood loss, poor nutritional intake, or a bleeding disorder. A thorough evaluation of the gastrointestinal tract for a source of blood loss, usually requiring a gastroenterology consultation for upper and lower GI endoscopy, should be undertaken, as iron-deficiency anemia may be the initial presentation of a GI malignancy.

Anemia with an elevated MCV, macrocytic anemia, is most often a manifestation of folate or vitamin B_{12} deficiency. The presence of macrocytic anemia, with or without the symptoms previously mentioned, should lead to further testing to determine B_{12} and folate levels. An elevated methylmalonic acid (MMA) level can be used to confirm a vitamin B_{12} deficiency. Folate deficiency anemia is usually seen in alcoholics, whereas B_{12}-deficiency anemia mostly occurs in people with pernicious anemia, a history of gastrectomy, diseases associated with malabsorption (eg, bacterial infection, Crohn disease, celiac disease), and strict vegans (rare).

In the elderly, anemia of chronic inflammation (formerly known as anemia of chronic disease) is the most common cause of a normocytic anemia. Anemia of chronic inflammation is anemia that is secondary to some other underlying condition. Along with causing a normocytic anemia, anemia of chronic disease can also present as a microcytic anemia. This type of anemia can easily be confused with iron-deficiency anemia because of its similar initial laboratory picture. **In anemia of chronic inflammation, the body's iron stores are normal, but the capability of using the stored iron in the reticuloendothelial system becomes decreased**. A lack of improvement in symptoms and hemoglobin

Table 9–1 LABORATORY VALUES DIFFERENTIATING IRON-DEFICIENCY ANEMIA FROM ANEMIA OF CHRONIC INFLAMMATION

TEST	IRON DEFICIENCY	ANEMIA OF CHRONIC INFLAMMATION
Serum iron	Low	Low or normal
TIBC	High	Low
Transferrin saturation	Low	Low or normal
Serum ferritin	Low	Normal or high

level with iron supplementation are important clues indicating that the cause is chronic disease and not iron depletion, regardless of the laboratory picture. Another cause of normocytic anemia is renal insufficiency due to decreased erythropoietin production. Although bone marrow iron store remains the gold standard to differentiate between iron-deficiency anemia and anemia of chronic disease, simple serum testing is still used to diagnose and differentiate these two types of anemia (Table 9–1).

Treatment

The treatment of anemia is determined based on the type and cause of the anemia. Any cause of anemia that creates a hemodynamic instability can be treated with a red blood cell transfusion. A hemoglobin less than 7 g/dL is a commonly used threshold for transfusion, however transfusion may be indicated at higher levels if the patient has a comorbid condition such as coronary artery disease. Iron-deficiency anemia is treated first by identification and correction of any source of blood loss. Most iron deficiency can be corrected by oral iron replacement. Various iron preparations are available; a typical treatment is ferrous sulfate 325 mg three times a day. Parenteral iron preparations are available for those with poor iron absorption and high iron replacement needs. Vitamin B_{12} deficiency traditionally has been treated by intramuscular B_{12} therapy with a regimen of 1000 μg IM daily for 7 days, then weekly for 4 weeks, then monthly for the rest of the patient's life. Newer research shows that many patients can be successfully treated with oral B_{12} therapy using 1000 to 2000 μg po in a similar regimen. Folate deficiency can be treated with oral therapy of 1 mg daily until the deficiency is corrected. Anemia of chronic inflammation is managed primarily by treatment of the underlying condition.

Comprehension Questions

9.1 A 58-year-old woman comes to your office complaining of fatigue. She has also noticed a burning sensation in her feet over the past 6 months. A CBC shows anemia with an increased MCV. Which of the following is the most likely cause of her anemia?

A. Lack of intrinsic factor
B. Inadequate dietary folate
C. Strict vegetarian diet
D. Chronic GI blood loss

9.2 A 65-year-old man with a history of rheumatoid arthritis is found to have a microcytic anemia. He had a colonoscopy 1 year ago which was normal and stool guaiac is negative. Which of the following is the most likely cause of his anemia?

A. Iron deficiency
B. Chronic disease
C. Pernicious anemia
D. Folate deficiency

Match the following lab pictures (A-D) of patients with anemia with the cases described in questions 9.3 to 9.4:

A. Normal MMA; decreased serum folate level
B. Elevated MMA; decreased serum B_{12} level
C. Elevated ferritin; normal MCV; decreased serum iron level
D. Decreased ferritin; decreased MCV; decreased serum iron level

9.3 A 68-year-old male is found to have an incidental finding of anemia while in the hospital for alcohol abuse.

9.4 A 67-year-old male with dizziness and a positive stool guaiac test.

9.5 A 68-year-old man is found to have an incidental finding of anemia while hospitalized with pneumonia. His physical examination is normal except for crackles in the left lower lobe. Serum laboratory examinations reveal a normal MMA and a decreased serum folate level. Which of the following is the best next step?

A. Administer CAGE questionnaire
B. Esophagogastroduodenoscopy
C. Serum iron assay
D. Neurology Consultation

ANSWERS

9.1 **A.** The clinical presentation and CBC findings are consistent with macrocytic anemia due to B_{12} deficiency. Pernicious anemia (lack of intrinsic factor) is the most common cause. B_{12} deficiency can also be seen in patients who follow a strict vegetarian diet, however the body's B_{12} stores can last several years before they are depleted.

9.2 **B.** Anemia of chronic disease can cause normocytic or microcytic anemia, and may be secondary to rheumatoid arthritis in the patient. Iron deficiency anemia is less likely with a normal colonoscopy and negative stool guaiac, and serum iron studies could be used to help differentiate the two.

9.3 **A.** Alcohol abuse is a common cause of folate deficiency. A normal MMA level essentially rules out a concomitant vitamin B_{12} deficiency.

9.4 **D.** Low serum iron, low MCV, and low ferritin levels, along with a finding of blood in the stool, are consistent with iron-deficiency anemia. A workup for the source of the GI blood loss should ensue.

9.5 **A.** Alcohol abuse, which may be assessed by the CAGE questionnaire, is a common cause of folate deficiency. CAGE is an acronym which stands for Cut back, Annoyed, Guilty, and Eye-opener. A normal MMA level essentially rules out a concomitant vitamin B_{12} deficiency. Gastric endoscopy—to look for atrophic gastritis—would be indicated for pernicious anemia. A serum iron assay would likely be high because of increased turnover of iron in patients with megaloblastic anemia due to either B_{12} or Folate deficiency. A neurology consultation would be needed if the patient had neurologic signs or symptoms of B_{12} deficiency.

Clinical Pearls

- Conjunctival pallor is an indication for anemia workup in elderly patients.
- Clinical findings of anemia require investigation for underlying causes.
- GI bleeding is an important cause of iron-deficiency anemia in both female and male geriatric patients; this type of anemia mandates a GI workup in this patient population.
- Investigating for vitamin B_{12} and folate deficiency is of high importance in a patient with a history of heavy EtOH (ethyl alcohol) intake and/or abuse.

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Case 10

A 40-year-old man presents to the clinic complaining of having 10 episodes of watery, nonbloody diarrhea that started last night. He vomited twice last night but has been able to tolerate liquids today. He has had intermittent abdominal cramps as well. He reports having muscle aches, weakness, headache, and low-grade temperature. He is here with his daughter, who started with the same symptoms this morning. On questioning, he states that he has no significant medical history, no surgeries, and does not take any medications. He does not smoke cigarettes, drink alcohol, use any illicit drugs, and has never had a blood transfusion. He and his family returned to the United States yesterday, following a week-long vacation in Mexico.

On examination, he is not in acute distress. His blood pressure is 110/60 mm Hg, his pulse is 98 beats/min, his respiratory rate is 16 breaths/min, and his temperature is 99.1°F (37.2°C). His mucous membranes are dry. His bowel sounds are hyperactive and his abdomen is mildly tender throughout, but there is no rebound tenderness and no guarding. A rectal examination is normal and his stool is guaiac negative. The remainder of his examination is unremarkable.

- What is the most likely diagnosis?
- What would you do next?
- What are potential complications?

ANSWERS TO CASE 10:
Acute Diarrhea

Summary: A 40-year-old man who recently returned from Mexico with profuse, acute, nonbloody diarrhea and dry mucous membranes on examination, which are consistent with developing dehydration. An ill family member with identical symptoms suggests an infectious cause of this acute illness.

- **Most likely diagnosis:** Acute gastroenteritis
- **Next step:** Order stool for fecal leukocytes
- **Potential complication:** Dehydration and electrolyte abnormalities

ANALYSIS

Objectives

1. To clearly understand when and how to do a workup for acute diarrhea, considering the most probable etiologies of diarrhea such us virus, *Escherichia coli*, *Shigella*, *Salmonella*, *Giardia*, and amebiasis.
2. To understand the role of fecal leukocytes and stool occult blood in the evaluation of acute diarrhea.
3. To understand that volume replacement and correction of electrolyte abnormalities are a key component in the treatment and prevention of diarrhea complications.

Considerations

This 40-year-old man developed severe diarrhea, nausea, and vomiting. His **most immediate problem is volume depletion,** as evidenced by his dry mucous membranes. The priority is to **replace the lost intravascular volume, usually with intravenous normal saline.** Electrolytes and renal function should be evaluated and abnormalities corrected. While correcting and/or preventing further dehydration, you need to determine the etiology of the diarrhea. Up to **90% of acute diarrhea is infectious** in etiology. He does not have any history compatible with chronic diarrhea, causes of which include Crohn disease, ulcerative colitis, gluten intolerance, irritable bowel syndrome, and parasites. He had been in Mexico recently, which predisposes him to different pathogens: *E coli*, *Campylobacter*, *Shigella*, *Salmonella*, and *Giardia*. He does not have bloody stools. The **presence of blood in the stool would suggest an invasive bacterial infection,** such as hemorrhagic or enteroinvasive *E coli* species, *Yersinia* species, *Shigella*, and *Entamoeba histolytica*.

Examination of the stool for leukocytes is a simple, inexpensive test that helps to differentiate between the types of infectious diarrhea. If leukocytes

are present in the stool, the suspicion is higher for *Salmonella, Shigella, Yersinia*, enterohemorrhagic and enteroinvasive *E coli, Clostridium difficile, Campylobacter,* and *Entamoeba histolytica*. In general, ova and parasite evaluation is unhelpful, unless the history strongly points toward a parasitic source or the diarrhea is prolonged.

The majority of the diarrheas are viral, self-limited, and do not need further evaluation. In this particular patient, because of his recent travel to Mexico, traveler's diarrhea should be strongly considered and treated with the appropriate antibiotic.

APPROACH TO
Acute Diarrhea

DEFINITIONS

ACUTE DIARRHEA: Diarrhea present for less than 2-week duration.

CHRONIC DIARRHEA: Diarrhea present for longer than 4-week duration.

DIARRHEA: Passage of abnormally liquid or poorly formed stool in increased frequency.

SUBACUTE DIARRHEA: Diarrhea present for 2- to 4-week duration.

CLINICAL APPROACH

Etiologies

Approximately 90% of acute diarrhea is caused by infectious etiologies, with the remainder caused by medications, ischemia, and toxins. Infectious etiologies often depend on the patient population. **Travelers to Mexico** will frequently contract **enterotoxigenic** *E coli* as a causative agent. **Traveler's diarrhea** is a common entity and can be induced by a variety of bacteria, viruses, and parasites (See Table 10–1). Campers are often affected by *Giardia*.

Table 10–1 COMMON ETIOLOGIES OF TRAVELER'S DIARRHEA

BACTERIA	VIRUSES	PARASITES
E coli (all types) *Salmonella* *Shigella* Vibrio non-cholera *Campylobacter*	Rotavirus Norovirus	*Giardia lamblia* *E histolytica* *Cryptosporidium parvum*

Consumption of foods is also frequently a culprit. ***Salmonella* or *Shigella*** can be found in **undercooked chicken,** enterohemorrhagic *E coli* from undercooked hamburger, and *Staphylococcus aureus* or *Salmonella* from **mayonnaise.** Raw seafood may harbor *Vibrio, Salmonella*, or hepatitis A. Sometimes the **timing** of the **diarrhea** following food ingestion is helpful. For example, **illness within 6 hours of eating a salad containing mayonnaise suggests *S aureus*, within 8 to 12 hours suggests *Clostridium perfringens*, and within 12 to 14 hours suggests *E coli*.**

Daycare settings are particularly common for *Shigella, Giardia*, and rotavirus to be transmitted. Patients in nursing homes, or who were recently in the hospital, may develop *Clostridium difficile* colitis from antibiotic use.

Clinical Presentation

Most patients with acute diarrhea have self-limited processes and do not require much workup. Exceptions to this rule include profuse diarrhea, dehydration, fever exceeding 100.4°F (38.0°C), bloody diarrhea, severe abdominal pain, duration of the diarrhea for more than 48 hours, and children, elderly patients, and immunocompromised patients. Traveler's diarrhea is characterized by greater than 3 loose stools in a 24-hour period accompanied by abdominal cramping, nausea, vomiting, fever, or tenesmus. Most cases occur within the first 2 weeks of travel.

Past and recent medical history should include exposures to medications and foods, travel history, and coworkers, classmates, or family members with similar symptoms. A history of a viral illness may provide a clue to the etiology. The initial evaluation should determine if the patient can tolerate oral intake. The patient who is both vomiting and having diarrhea is more prone to dehydration and more likely to need hospital admission for IV hydration.

The physical examination should focus on the vital signs, clinical impression of the volume status, and abdominal examination. Volume status is determined by observing whether the mucous membranes are moist or dry, the skin has good turgor, and the capillary refill is normal or delayed. The principal laboratory test is the stool for microscopic and microbiologic examination; usually it is sent for culture, but these results generally require several days to obtain and are not useful in the acute setting. Ova and parasite evaluation is generally unhelpful, except in selected circumstances of very high suspicion. Stool for *Clostridium difficile* toxin may yield the etiology in patients who develop symptoms after antibiotic use. Although classically associated with clindamycin, **any antibiotic can cause pseudomembranous colitis.** A complete blood count, electrolytes, and renal function tests are sometimes indicated.

Treatment

Most cases of diarrhea resolve spontaneously in a few days without treatment. Replacement of fluids and electrolytes is the first step in treating the

consequences of acute diarrhea. For mildly dehydrated individuals who can tolerate oral fluids, solutions such as the World Health Organization oral rehydration solution or commercially available drinks such as Pedialyte or Gatorade, often are all that is needed. Those with more serious volume deficits, elderly patients, and infants generally require hospitalization and intravenous hydration. If a parasitic infection is the cause of the diarrhea, prescription antibiotics may ease the symptoms. Antibiotics sometimes, but not always, help ease symptoms of bacterial diarrhea. However, antibiotics will not help viral diarrhea, which is the most common kind of infectious diarrhea. Over-the-counter medications may help to slow down the frequency of the stools, but they do not speed the recovery. Certain infections may be made worse by over-the-counter medications because they prevent your body from getting rid of the organism that is causing the diarrhea.

Prevention

Hand washing is a simple and effective way to prevent the spread of viral diarrhea. Adults, children, and clinic and hospital personnel should be encouraged to wash their hands. Because viral diarrhea spreads easily, children with diarrhea should not attend school or child care until their illness has resolved.

To prevent diarrhea caused by contaminated food, use dairy products that have been pasteurized. Serve food immediately or refrigerate it after it has been cooked. Do not leave food out at room temperature because it promotes the growth of bacteria.

Travelers to locations, such as developing countries, where there is poor sanitation and frequent contamination of food and water, need to be cautious to reduce their risk of developing diarrhea. They should be advised to eat hot and well-cooked foods, and to drink bottled water, soda, wine, or beer served in its original container. Avoid drinks served over ice. Beverages from boiled water, such as coffee and tea, are usually safe. Recommend the use of bottled water even for teeth brushing. Also recommend avoiding raw fruits and vegetables unless they are peeled by the consumer immediately before being eaten. Patient's should avoid tap water and ice cubes.

Traveler's Prophylaxis and Treatment

The **best method for preventing traveler's diarrhea (TD) is to avoid contaminated food and water.** Antibiotic prophylaxis is not indicated unless the patient is at increased risk for complications from diarrhea or dehydration, such as underlying inflammatory bowel disease, renal disease, or an immunocompromised state. Fluoroquinolones are typically used for prophylaxis.

When antibiotics are indicated, therapy with a quinolone antibiotic should be started as soon as possible after the diarrhea begins. Most commonly, **ciprofloxacin (500 mg twice daily) is given for 1 or 2 days.** Quinolones

cannot be used in children or pregnant women. Quinolones will resolve the diarrheal symptoms in the majority of patients within 1 day. **Azithromycin,** given as a single 1000-mg dose in adults or 10 mg/kg daily for 3 days in children, is another effective drug for the treatment of TD. Azithromycin also can be used in pregnant women with traveler's diarrhea. **Rifaximin** can be used in TD caused by noninvasive strains of *E coli*. However, Rifaximin is not effective against infections associated with fever or blood in the stool.

Trimethoprim-sulfamethoxazole and ampicillin were popular drugs used in the past to treat TD, but increased resistance limits their use at this time. Bismuth subsalicylate is not recommended because, to be effective, it needs to be taken in large amounts that can cause salicylate toxicity.

Comprehension Questions

10.1 Several friends develop vomiting and diarrhea 6 hours after eating food at a private party. Which of the following is the most likely etiology of the symptoms?

A. Rotavirus
B. *Giardia*
C. *E coli*
D. *S aureus*
E. *Cryptosporidium*
F. *Vibrio*
G. *Excessive alcohol*

10.2 A 40-year-old man travels to Mexico and develops diarrhea 1 day after coming back to the United States. Which of the following is the most likely etiology of the symptoms?

A. Rotavirus
B. *Giardia*
C. *E coli*
D. *S aureus*
E. *Cryptosporidium*
F. *Vibrio*

10.3 A young woman eats raw seafood and 2 days later develops fever, abdominal cramping, and watery diarrhea. Which of the following is the most likely etiology of the symptoms?

A. Rotavirus
B. *Giardia*
C. *E coli*
D. *S aureus*
E. *Cryptosporidium*
F. *Vibrio*

10.4 During the winter, a young daycare worker develops watery diarrhea. Which of the following is the most likely etiology of the symptoms?
A. Rotavirus
B. *Giardia*
C. *E coli*
D. *S aureus*
E. *Cryptosporidium*
F. *Vibrio*

10.5 A 45-year-old man presents with 3 days of watery diarrhea and abdominal cramping. He has no sick contacts and has not traveled recently. He is not currently taking any medications, but he was prescribed amoxicillin 2 weeks ago for a sinus infection. Which of the following tests is most likely to identify the cause of his diarrhea?
A. Stool Guaiac
B. Evaluation of stool for fecal leukocytes
C. Evaluation of stool for ova and parasites
D. Clostridium difficile toxin immunoassay

10.6 In the patient described in question 10.5, which of the following is the treatment of choice for his diarrhea?
A. Ciprofloxacin
B. Azithromycin
C. Metronidazole
D. Loperamide

ANSWERS

10.1 **D.** *S aureus* toxin usually causes vomiting and diarrhea within a few hours of food ingestion.

10.2 **C.** *E coli* is the most common etiology for traveler's diarrhea.

10.3 **F.** *Vibrio* is a common cause of diarrhea among people who eat raw sea food.

10.4 **A.** Rotavirus is a common etiology for watery diarrhea, especially in the winter.

10.5 **D.** Although any antibiotic can cause C *difficile* colitis, clindamycin, cephalosporins, and penicillins are the most commonly implicated.

10.6 **C.** Metronidazole or oral vancomycin can be used to treat C *difficile*. Ciprofloxacin and azithromycin can be used for treatment of traveler's diarrhea. Loperamide can decrease the frequency of bowel movements but is contraindicated in any patient with suspected C *difficile* colitis.

Clinical Pearls

- Most acute diarrheas are self-limited.
- Be cautious when assessing diarrhea in a child, elderly patient, or immunosuppressed host.
- Dehydration, bloody diarrhea, high fever, and diarrhea that do not respond to therapy after 48 hours are warning signs of possible complicated diarrhea.
- In general, acute, uncomplicated diarrhea can be treated with oral electrolyte and fluid replacement.

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Case 11

A 50-year-old Caucasian woman, new to your practice, presents for an "annual physical examination." She reports that she is very healthy, generally feels well and has no specific complaints. She has a history of having had a "partial hysterectomy," by which she means that her uterus and cervix were removed but her ovaries were left in place. The surgery was performed because of fibroids. She has had a Pap smear every year since the age of 18, all of which have been normal. She has had annual mammograms since the age of 40, all of which have been normal. She has no other significant medical or surgical history. She takes a multivitamin pill daily but no other medications. Her family history is significant for breast cancer that was diagnosed in her maternal grandmother at the age of 72. The patient is married, monogamous, and does not smoke cigarettes or drink alcohol. She tries to avoid dairy products because of "lactose intolerance." She walks 3 miles four times a week for exercise. Her physical examination is normal.

- For this patient, how often should a Pap smear be performed for cervical cancer screening?
- What could you recommend to reduce her risk of developing osteoporosis?
- What is the recommended interval for screening mammography?

ANSWERS TO CASE 11:
Health Maintenance in Adult Female

Summary: A 50-year old woman with a history of having had a hysterectomy for a benign indication comes to your office for a routine health maintenance visit.

- **Interval for cervical cancer screening:** Based upon her history of having a hysterectomy for benign disease and her overall low-risk status, cervical cancer screening can be discontinued in this patient.
- **Interventions to reduce her risk of developing osteoporosis:** Supplementation with at least 1200 mg calcium and 400 to 800 IU vitamin D daily; regular weight-bearing exercise.
- **Recommended interval for screening mammography in a 50-year-old woman:** Annual.

ANALYSIS

Objectives

1. Discuss age appropriate preventive health measures for adult women.
2. Review evidence in support of specific health maintenance measures.

Considerations

When evaluating patients for preventive health measures, there should not be a "one size fits all" approach to care. Some interventions are appropriate across age groups; some are age or risk-factor specific and should be tailored accordingly. Interventions to consider include screening for cardiovascular disease, breast cancer, cervical cancer, osteoporosis, and domestic violence. Other health maintenance measures, such as screening for colon cancer and routine adult immunizations are discussed in Case 1 and tobacco use is discussed in Case 7. The interventions discussed in this chapter are primarily based upon recommendations of the United States Preventive Services Task Force (USPSTF); recommendations of other expert panels or advocacy organizations are included where appropriate.

APPROACH TO
Health Maintenance in Women

DEFINITIONS

BRCA: Abbreviation for genes associated with breast cancer and ovarian cancer. Mutations in the BRCA1 or BRCA2 genes can be associated with a three- to sevenfold increased risk for breast cancer, along with increased risks of ovarian, colorectal, and possibly other types of cancer.

WOMEN'S HEALTH INITIATIVE: An NIH sponsored research program to address the most common causes of morbidity and mortality in postmenopausal women. This initiative included clinical trials of the effect of hormone therapy on the development of heart disease, fractures, and breast cancer.

CLINICAL APPROACH

Cardiovascular Disease in Women

Cardiovascular diseases are the number one killer of women in the United States. Many of the cardiovascular disease risk factors in women are the same as those in men: hypertension, high LDL (low-density lipoprotein)-cholesterol, tobacco use, diabetes mellitus, family history of cardiovascular disease. As such, the **USPSTF screening recommendations for cardiovascular disease for women are similar to those for men.** All women aged 18 and older should be screened for hypertension by the measurement of blood pressure (Level A recommendation). Further, all women aged 45 and older should be screened for lipid disorders (Level A recommendation). Abnormally elevated blood pressure or serum lipids should be managed appropriately.

An area of cardiovascular disease risk unique to women is in postmenopausal hormone replacement. Many women have taken hormone replacement therapy for relief of vasomotor symptoms ("hot flashes") and reduction of risk of developing osteoporosis. Recent studies, most notably the Women's Health Initiative, have shown **increased rates of adverse cardiovascular outcomes in women taking either estrogen alone or combined estrogen and progesterone.** These risks include an increased risk of coronary heart disease, stroke, and venous thromboembolic disease. For this reason, the use of hormone replacement therapy for the prevention of chronic conditions is not advised (Level D recommendation) and **any use of hormone replacement should be of the lowest effective dose for the shortest effective time period.**

Screening for Breast Cancer

Breast cancer is second to lung cancer in number of cancer-related deaths in women. There are approximately 190,000 new cases and over 40,000 deaths per year from breast cancer in the United States. The incidence increases with age; other risk factors include having the first child after the age of 30, a family history of breast cancer (particularly if in the mother or sister), personal history of breast cancer or atypical hyperplasia found on a previous breast biopsy, or a known carrier of the BRCA-1 or BRCA-2 gene.

The process of screening for breast cancer generally includes consideration of three modalities: the breast self examination (BSE), the clinical breast examination (CBE) performed by a health care professional, and mammography. Other modalities, including ultrasonography and magnetic resonance imaging (MRI), are available but currently they are not widely recommended for screening purposes. Upon review of the available studies, the USPSTF has determined that, at this time, there is insufficient evidence to recommend either the CBE or BSE (Level A recommendation). Both BSE and CBE may be associated with increased risks of false-positive results and subsequent need for biopsies while evidence is lacking that they reduce breast cancer mortality. Studies regarding both are ongoing.

Mammography screening every 12 to 33 months has been shown to reduce mortality from breast cancer. The **benefits of routine mammographic screening increase with age,** as the incidence of breast cancer is higher in older women. There is not an age cut off to stop screening, but a discussion about continuing screening can be considered in the older woman with significant co-morbid conditions that may limit her life expectancy. Part of the discussion regarding mammography also includes the risk of false-positive or false-negative (less common) results and need for additional interventions, such as breast biopsy. **Most abnormalities found on mammography are not breast cancer** but require further evaluation to make that determination. The USPSTF advises screening with mammography, beginning at the age of 40 for the general population, with a recommended interval of every 1 to 2 years (Level B recommendation). Recommendations are also available from other organizations, including the American Cancer Society, American Academy of Family Physicians, and American College of Obstetricians and Gynecologists, which advocate annual mammography after the age of 50. Their recommendations for women aged 40 to 49 vary, but generally advise screening every 1 to 2 years.

Screening for Cervical Cancer

Cervical cancer is the tenth leading cause of cancer death in women in the United States, with 3670 deaths in 2007. **The incidence of cervical cancer has fallen dramatically since the introduction of the Pap smear as part of routine screening.** Risk factors for cervical cancer include early onset of sexual intercourse, multiple sexual partners, human papilloma virus (HPV) infection with high-risk subtype of HPV (HPV viral types 16, 18, 45, 56), and tobacco use.

The optimal age to begin screening is unclear, but the USPSTF recommends starting at age 21 or within 3 years of the onset of sexual activity, whichever comes first (Level A recommendation). While there is limited utility in screening for cervical cancer in a person who has never been sexually active, many organizations will advocate an age-based approach because of high rates of sexual activity by a certain age and because health-care providers may not always get accurate sexual histories.

Most cases of cervical cancer occur in women who either have not been screened in over 5 years or did not have follow-up after an abnormal Pap smear. The optimal screening interval between Pap smears is not known. Based upon the available studies, the USPSTF has not found evidence that annual screening is better at reducing morbidity and mortality from cervical cancer than screening every 3 years. The American Cancer Society recommends annual Pap smears until age 30 and then spacing out the interval to every 2 to 3 years; other groups suggest spacing out the interval after three consecutive normal Pap smears.

A vaccine against high-risk HPV subtypes has recently become available. It is indicated for use in girls and women aged 9 through 26. To date, there is no recommendation to alter the Pap smear screening intervals for women who have been vaccinated against HPV.

The purpose of a Pap smear is to detect precancerous cervical changes or possible cases of cervical cancer early, in order to improve the odds of survival. Keeping this in mind, the USPSTF recommends against Pap smears for women who have had a hysterectomy (including removal of the cervix) for benign indications (Level D recommendation). It is prudent to ask a woman who has had a hysterectomy why the surgery was performed and to confirm (either by reviewing the operative report or on examination) the absence of the cervix. A woman who had a hysterectomy for cancerous indications falls out of the general screening parameters discussed here.

The optimal age to stop screening is subject to debate. The USPSTF discusses discontinuing cervical cancer screening after the age of 65 both if no new risk factors have been identified (ie, new partner) and if there has been adequate recent screening. The incidence of cervical cancer falls with age; the false positive rate increases, thus potentially subjecting women to additional unnecessary procedures. The American Cancer Society recommends that screening may be stopped at the age of 70 if a woman has had three consecutive normal Pap smears and no abnormal Pap smears in the last 10 years.

Screening for Osteoporosis

Osteoporosis is a condition of decreased bone mineral density associated with an increased risk of fracture. **Half of all postmenopausal women will have an osteoporosis related fracture in their lifetime.** These include hip fractures, which are associated with higher risks of loss of independence, institutionalization, and death. The risk of osteoporosis is increased with advancing age,

tobacco use, low body weight, Caucasian or Asian ancestry, family history of osteoporosis, low calcium intake, and sedentary lifestyle.

Osteoporosis may also occur in men, although with a lower incidence than it does in women. Along with the risk factors noted above, the prolonged use of corticosteroids, presence of diseases that alter hormone levels (such as chronic kidney or lung disease), and undiagnosed low testosterone levels increase the risk of osteoporosis in men.

Screening for osteoporosis is done by measurement of bone density. Measurement of the hip bone density by dual-energy x-ray absorptiometry (DXA) is the best predictor of hip fracture. Measurement of bone density is compared to the bone density of young adults and the result is reported as standard deviation from the mean bone density of the young adult (T-score). Osteoporosis is present if the patient's T-score is at or below −2.5 (ie, measurement of the patient's bone density is more than 2.5 standard deviations below the young adult mean); osteopenia is present if the T-score is between −1.0 and −2.5. Other modalities, such as measurement of wrist or heel density, single-energy x-ray absorptiometry, and ultrasound are being evaluated and may have some short-term predictive value. The USPSTF recommends screening for osteoporosis via DXA in women after the age of 65 and considering screening in women aged more than 60 with higher risk of osteoporosis-related fractures (Level B recommendation).

Calcium and vitamin D intake have a role in the prevention and treatment of osteoporosis. The National Osteoporosis Foundation (NOF) recommends at least **1200 mg of calcium and 400 to 800 IU of vitamin D per day for all women over the age of 50.** If dietary intake is not sufficient, supplements may be used. Weight-bearing and muscle strengthening exercise is also recommended both for its direct effects on increasing bone density and for its benefits in strength, agility, and balance, which may reduce the risk of falls.

When osteoporosis is diagnosed, patients should be treated with calcium, vitamin D, exercise and strategies should be implemented to reduce the risk of falls. These strategies include evaluation and treatment, if needed, of vision and hearing deficits, management of medical disorders that can promote falls (movement disorders, neurological disorders, etc), and periodic evaluation of medications taken that may affect balance or movement. Hip protectors may be beneficial in those at high risk for falls.

Medications used for the prevention and treatment of osteoporosis are included in Table 11–1.

Screening for Domestic Violence

Estimates indicate that between 1 and 4 million women are sexually, physically, or emotionally abused by an intimate partner each year. Women are also much more likely to be abused by an intimate partner than men. Multiple factors are associated with intimate partner violence and include young age, low income status, pregnancy, mental illness, alcohol or substance use by victims or

Table 11–1 MEDICATIONS FOR THE PREVENTION AND TREATMENT OF OSTEOPOROSIS

CLASS/ MEDICATION	OSTEOPOROSIS-RELATED INDICATIONS	DOSAGE	SIDE EFFECTS
Bisphosphonates			Esophagitis, gastritis, swallowing difficulty; all bisphosphonates should be taken on anempty stomach with a full glass of water and the patient should stay upright for at least 30 min after taking the pill
Alendronate (Fosamax)	Prevention and treatment	Prev: 5 mg daily or 35 mg weekly Tx: 10 mg daily or 70 mg weekly	
Risedronate (Actonel)	Prevention and treatment	Prev and Tx: 5 mg daily or 35 mg weekly or 150 mg monthly	
Ibandronate (Boniva)	Prevention and treatment	Prev and Tx: 150 mg monthly	
Calcitonin (Miacalcin [inj or NS])	Treatment	IM/SC: 100 units daily Nasal: 1 spray (200 units) daily	Inj: flushing, injection site reaction NS: nosebleeds, nasal irritation
Estrogen (Numerous)	Prevention	Varies	Potential increased risk of DVT, MI, stroke, PE
Parathyroid hormone Teriparatide (Forteo)	Treatment	20 micrograms SC daily	Leg cramps, dizziness, transient hypercalcemia
Selective estrogen receptor modulator Raloxifene (Evista)	Prevention and treatment	60 mg daily	Hot flashes, weight gain, DVT/PE

Abbreviations: DVT, deep venous thrombosis; Inj, injection; MI, myocardial infarction; NS, nasal spray; PE, pulmonary embolism; Prev, prevention; SC, subcutaneous Tx, treatment.

partner, separated or divorced status, and a history of childhood sexual/physical abuse. Multiple rating scales are available to assess for presence of domestic violence which are of variable quality. The USPSTF found insufficient evidence to recommend for or against routine screening for intimate partner abuse, or that screening affects outcomes (Level A recommendation). Other groups, including the American Academy of Family Physicians and American Medical Association, recommend awareness and advocate asking about domestic violence. Documentation and treatment of injuries, counseling and information regarding protective services are part of the evaluation when domestic violence is suspected. Reporting of domestic violence is mandatory in several states; be aware of the requirements of your state.

Comprehension Questions

11.1 A 21-year-old woman presents for her first Pap smear. She received the full HPV vaccine series at age 19. Assuming that her examination and Pap smear results are normal, when would you recommend that she return for a follow-up Pap smear?

A. 6 months, as the first Pap smear should be followed up soon to reduce the false-negative rate associated with this screening test
B. 1 year, as she should have at least three normal smears before going to a longer interval
C. 3 years, as the Pap smear was normal
D. 5 years, as she is at low risk because she received the HPV vaccine

11.2 Which of the following situations is associated with an increased risk of intimate partner violence?

A. Pregnancy
B. Older age
C. Higher income
D. Married status

11.3 Which of the following statements regarding osteoporosis is most accurate?

A. Fewer than 25% of women will have an osteoporosis-related fracture in their lifetime.
B. Long-term therapy with a combination of estrogen and progesterone is recommended for the treatment of postmenopausal osteoporosis.
C. African-American women have an increased risk of osteoporosis.
D. 1200 mg of calcium and 400 to 800 IU vitamin D, through diet or supplement, is recommended for all women aged more than 50.

11.4 A 48-year-old woman presents for a well-woman examination. She notes that she had a "partial" hysterectomy in the past. Your records reveal that she had her uterus removed, but the cervix and ovaries were left in place. You also note that she has had annual Pap smears for the last 5 years and that all were normal. She read on the internet that women who have had a hysterectomy no longer need Pap smears. Which of the following would be your advice?

A. "You no longer need to get Pap smears."
B. "You should continue to have annual Pap smears."
C. "You should continue to have Pap smears but can space out the interval to 3 years."
D. "You should continue with annual Pap smears until the age of 50. If they are all normal, you can stop having them at that time."

ANSWERS

11.1 **B.** The optimal cervical cancer screening interval is not known, however most authorities recommend at least three normal, annual Pap smears prior to spacing out the screening interval. The use of HPV vaccine is not an indication to alter cervical cancer screening recommendations at this time.

11.2 **A.** Intimate partner violence can occur in any relationship, but the risk is increased in certain situations, which include young age, low income status, pregnancy, mental illness, alcohol or substance use by victims or partner, separated or divorced status, and a history of childhood sexual/physical abuse.

11.3 **D.** Women aged more than 50 should be advised to have a daily intake of 1200 mg or more of calcium and 400 to 800 IU of vitamin D and to participate in regular weight-bearing and muscle-building exercise. Approximately half of all women will have an osteoporosis-related fracture. Hormone replacement therapy should be of the lowest effective dose for the shortest effective time, due to the increased risk of adverse cardiovascular and thromboembolic complications. Asian and Caucasian women are at higher risk of osteoporosis than African-American women.

11.4 **C.** Women who have had a hysterectomy, including removal of the cervix, for benign indications can usually discontinue Pap smear screening. Women who still have a cervix should continue with screening for cervical cancer. Women who have a hysterectomy for cervical dysplasia should continue to have annual Pap smears. This woman, who has had at least five normal Pap smears in a row, can safely be counseled that she may space out her screening interval to 3 years.

Clinical Pearls

- Most abnormalities found on mammography are not breast cancer.
- The number one killer of women in America is cardiovascular disease. Risk factors for cardiovascular diseases in women need to be managed as aggressively as they are in men.

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Case 12

A 25-year-old man presents to your office on a Monday morning with ankle pain. He was playing in his usual Saturday afternoon basketball game when he injured his right ankle. He says that he jumped for a rebound and landed on another player's foot. His right ankle "rolled over," he fell to the floor, and his ankle immediately started to hurt. He did not hear or feel a pop. He was able to stand and walk with a limp, but was unable to continue playing. His ankle swelled over the next day in spite of rest, icing, and elevation. He suffered no other injury from the fall. On examination, he is a healthy-appearing man with normal vital signs. The lateral aspect of the right ankle is swollen. The right ankle has normal dorsiflexion and plantar flexion and there is no focal tenderness to palpation of the fibula, malleoli, or foot. No ligamentous laxity is noted on testing. He can bear weight with minimal pain. There is normal sensation and capillary refill in the foot. The remainder of his examination is normal.

- What is the most likely diagnosis of this injury?
- What further diagnostic testing is needed at this time?
- What is the most appropriate therapy?

ANSWERS TO CASE 12:
Musculoskeletal Injuries

Summary: A 25-year-old man presents with an inversion injury of his right ankle that occurred during a basketball game. His ankle is swollen, but he is able to bear weight, and has no focal tenderness and no ligament laxity.

- **Most likely diagnosis:** Sprain of the right ankle.
- **Further diagnostic testing needed:** None at this time.
- **Most appropriate initial therapy:** "PRICE" therapy: **P**rotection, **R**est, **I**ce, **C**ompression, and **E**levation; a nonsteroidal anti-inflammatory drug (NSAID) or acetaminophen as needed for pain and early mobilization.

ANALYSIS

Objectives

1. Learn an approach to the diagnosis of musculoskeletal injuries.
2. Know when to order imaging tests and which test to order to evaluate musculoskeletal complaints.
3. Be able to manage common joint sprains and strains.

Considerations

Ankle sprains are the most common acute, sports-related injury, and are a common reason for visits to primary care physicians, urgent care centers, and emergency rooms. As in this case, **most ankle sprains are the result of inversion of an ankle that is plantar flexed**—landing on another player's foot in basketball, stepping in a hole or on uneven ground when running, missing a curb while walking. The lateral ankle is injured much more commonly than the medial ankle, as the bony anatomy of the tibiotalar joint and the very strong deltoid ligament complex protect the medial ankle from injury. The lateral ligaments—anterior talofibular ligament (ATFL), calcaneofibular ligament (CFL), and posterior talofibular ligament (PTFL)—are relatively weaker and more commonly injured. The **ATFL is the most commonly injured ligament,** followed by the CFL.

Ankle sprains are graded as grade 1, 2, or 3 injuries. A grade 1 sprain is stretching of the ATFL, which causes pain and swelling, but no mechanical instability and little to no functional loss. The patient can usually bear weight with, at most, mild pain. The history and examination of the patient in the case presented is consistent with a grade 1 ankle sprain. A grade 2 sprain represents a partial tear of the ATFL and stretching of the CFL. This injury causes more severe pain, swelling, and bruising. There is mild to moderate

joint instability, significant pain with weight bearing, and loss of range of motion. A grade 3 sprain is a complete tear of the ATFL and CFL with partial tearing of the PTFL. This injury causes significant joint instability, loss of function, and inability to bear weight.

The Ottawa Ankle Rules are a decision model designed to aid a physician in determining which patients with ankle injuries need an x-ray. These decision rules have been validated for nonpregnant adults who have a normal mental status, no other significant concurrent injury, and who are evaluated within 10 days of the injury. When properly applied, the **Ottawa Ankle Rules have a sensitivity approaching 100% in ruling out significant malleolar and midfoot fractures.** These rules show that x-rays of the ankle should be performed if there is bony tenderness of the posterior edge or tip of the distal 6 cm of either the medial or lateral malleolus, or if the patient is unable to bear weight immediately or when examined. Foot x-rays should be performed if there is bony tenderness over the navicular bone (medial midfoot), the base of the fifth metatarsal (lateral midfoot) or if the patient is unable to bear weight. The patient presented, who has no bony tenderness, no limitation in weight bearing, and no contraindication to the application of the decision rules, does not need imaging of his ankle or foot.

The management of ankle sprains should follow the pneumonic "PRICE"—Protection, Rest, Ice, Compression, and Elevation. Protection by appropriate splinting or casting can help to prevent further injury. Relative rest from activity also helps to promote ligament healing; although weight bearing can be allowed as tolerated and early, functional rehabilitation exercises are crucial. Ice applied as soon as possible after the injury helps to minimize swelling and relieve pain. Compression and elevation also promote reduction of swelling. In most cases, NSAIDs or acetaminophen are adequate for pain relief.

APPROACH TO
Sprains and Strains

DEFINITIONS

SPRAIN: A stretching or tearing injury of a ligament.

STRAIN: A stretching or tearing injury of a muscle or tendon.

CLINICAL APPROACH

History

As in all areas of medicine, the history of the presenting illness will guide the diagnostic workup. In the history of a patient with musculoskeletal complaints, important information to gather includes whether the primary symptom is

pain, limited movement, weakness, instability, or a combination of symptoms. The onset of the symptoms—whether acute, chronic, or an acute worsening of a chronic problem—can be significant. The location, severity, and pattern of radiation of pain should be delineated. Associated symptoms, such as numbness, should be identified. Efforts should be made to identify as specifically as possible the mechanism of any injury that led to the complaint. Interventions that have already been made, such as ice or heat, medications, splinting, and whether or not the interventions helped, should be noted.

Joint Examination

Examination of the musculoskeletal system should include documentation of inspection, palpation, range of motion, strength, neurovascular status, and, where appropriate, testing specific for the involved joint. Inspection should note the presence of swelling, bruising, deformity, and the use of any supports or assistive devices (eg, splints, crutches, bandages) that the patient is already using. **Examination of the unaffected limb can provide a good comparison and allow for subtle changes to be more easily identified.** Documentation should also be made of the patient's general functioning and mobility—does the patient walk with a limp, can the patient easily rise from a chair, is there difficulty getting on the examining table, is the patient's arm moving freely or held tightly to the patient's chest, and so on.

Palpation of the affected and surrounding areas can help to localize and confirm the presence of a specific injury. A focal area of bony tenderness may lead to the consideration of a fracture, whereas a tender, tight muscle may be more suggestive of a strain. The presence of joint effusions or soft-tissue swelling should be documented and may lead to consideration of specific injuries. Notation should be made of sensation, peripheral pulses, and capillary refill in the involved extremity. Absent pulses and delayed capillary refill, especially if the extremity is cool or cold, should prompt emergent evaluation and management of vascular insufficiency.

Range of motion should be tested both passively and actively. Active range of motion tests the patient's ability to move a joint. It tests the structural integrity of the joint, muscles, tendons, and neurologic impulses to the area and can be limited by problems with any of them or by the presence of pain. Passive range of motion tests the movement that an examiner can elicit in a relaxed patient. The presence of a dislocated joint or significant joint effusion may lead to limitations in both passive and active range of motion, where a torn tendon or muscle injury may have limited active, but preserved passive, range of motion.

Each joint or body area has specific examination maneuvers that can help to identify injury to specific structures. Table 12–1 lists some common maneuvers that are used to examine the shoulder, knee, and ankle.

Table 12–1 SPECIFIC TESTS FOR SHOULDER, KNEE, AND ANKLE EXAMINATIONS

TEST	STRUCTURE TESTED	RESULT IDENTIFIED (COMPARE TO UNAFFECTED SIDE)
Shoulder/Rotator Cuff		
Empty can test—with arm abducted, elbow extended, and thumb pointing down, patient elevates arm against resistance	Supraspinatus	Rotator cuff injury or tear
External rotation—with elbows at sides and flexed at 90°, patient externally rotates against resistance	Infraspinatus Teres minor	Rotator cuff injury or tear
Lift-off test—patient places dorsum of hand on lumbar back and attempts to lift hand off of back	Subscapularis	Rotator cuff injury or tear
Hawkins' impingement—pain with internal rotation when the arm is flexed to 90° with the elbow bent to 90°	Subacromial impingement	Rotator cuff injury or tear
Drop-arm rotator cuff—patient is unable to lower his arm slowly from a raised position		Large rotator cuff tear
Ankle		
Anterior drawer—examiner pulls forward on patient's heel while stabilizing lower leg with other hand	Anterior talofibular ligament	Excessive translation of joint suggests ATFL tear
Inversion stress test—examiner inverts ankle with one hand while stabilizing lower leg with other hand	Calcaneofibular ligament	Excessive translation or palpable "clunk" of talus on tibia suggests ligament tear
Squeeze test—examiner compresses tibia/fibula at midcalf	Syndesmosis	Pain at anterior ankle joint (below where examiner is squeezing) suggests syndesmotic injury

(*Continued*)

Table 12–1 SPECIFIC TESTS FOR SHOULDER, KNEE, AND ANKLE EXAMINATIONS (CONTINUED)

TEST	STRUCTURE TESTED	RESULT IDENTIFIED (COMPARE TO UNAFFECTED SIDE)
Knee		
Lachman test—knee in 20° flexion, examiner pulls forward on upper tibia while stabilizing upper leg	Anterior cruciate ligament	Excessive translation with no solid end point suggests tear
Anterior drawer—knee in 90° flexion, examiner pulls forward on upper tibia while stabilizing upper leg	Anterior cruciate ligament	Excessive translation with no solid end point suggests tear
Valgus stress—in full extension and at 30° flexion, medial-directed force on knee, lateral-directed force on ankle	Medial collateral ligament	Excessive translation suggests tear
Varus stress—in full extension and at 30° flexion, lateral-directed force on knee and medial-directed force on ankle	Lateral collateral ligament	Excessive translation suggests tear

Imaging

Following the history and examination, the physician must decide when it is necessary to perform x-rays or other imaging tests. Validated decision rules are available to aid in some of these decisions. The Ottawa Ankle Rules for the determination of when an x-ray is necessary in an ankle injury were discussed earlier in this case. Similarly, the Ottawa Knee Rules can aid in the determination of when to perform an x-ray in a knee injury. The Ottawa Knee Rules recommend performing a knee x-ray on patients with a knee injury who have any one of the following five criteria: (1) age 55 years or older, (2) isolated patella tenderness, (3) tenderness of the head of the fibula, (4) inability to flex the knee to 90°, and (5) inability to bear weight for four steps immediately and in the examination room (regardless of limping).

These rules were validated for, and should only be applied to, adults older than age 18 years, although further study suggests that they may be valid in younger ages.

When a decision is made to perform an imaging test, whether to acutely rule out a fracture or to evaluate an injury that is failing to improve, the **initial imaging study of choice is the plain x-ray.** At minimum, an x-ray series should include at least two views at 90° angles to each other. In patients with normal x-rays and continued symptoms, or with suspected ligament or tendon injuries of the shoulder, ankle, knee, or hip, magnetic resonance imaging (MRI) has largely supplanted other modalities as the imaging method of choice. MRI is highly sensitive and specific for articular or soft-tissue abnormalities, including ligament, tendon, and cartilage tears.

Management Principles

The initial management of most acute sprains and strains is "PRICE"—Protection from further injury, relative Rest, Ice to reduce swelling and pain, Compression, and Elevation to reduce edema. In most cases, NSAIDs or acetaminophen are adequate for pain control, with narcotics used only when necessary.

Numerous studies show that early mobilization of injured ligaments actually promotes healing and recovery. Range-of-motion exercises should be started as early as possible in patients with sprains and strains. For lower-extremity injuries, protected weight bearing with orthotics is allowable, with advancement to unsupported weight bearing as tolerated. Crutches may be necessary initially because of painful weight bearing.

The **most common cause of persistently stiff, painful, or unstable joints following sprains is inadequate rehabilitation.** All patients with sprain or strain injuries should be educated on the importance of rehabilitative exercises. When possible, handouts with a specific exercise program should be given to the patient when the patient is evaluated. If the patient is unsuccessful in accomplishing this on his own, referral for a formal physical therapy program can be beneficial.

Comprehension Questions

12.1 Based on the Ottawa Ankle Rules, which of the following situations is most appropriate to have radiographs of the involved bones?

A. A 6-year-old boy injures his ankle riding a scooter.
B. A 33-year-old woman injures both ankles and knees in a motor vehicle accident.
C. A 43-year-old man injured his ankle yesterday while playing volleyball.
D. A 22-year-old woman injures her ankle after falling while drunk.

12.2 A 32-year-old man comes for evaluation of right shoulder pain that he has had for the past 3 weeks. He thinks that he injured it playing softball but does not remember a specific injury. There is no bruising or swelling. He gets pain in the joint on external rotation and abduction, but has preserved range of motion. Which of the following is the initial imaging test of choice?

A. X-ray
B. MRI
C. CT scan
D. Arthrogram

12.3 A 45-year-old woman comes in for follow-up of an ankle sprain that occurred while she was jogging. X-rays done at your initial visit were negative for fracture. She has been unable to run because of persistent stiffness. Examination reveals no joint instability or focal tenderness. Which of the following is the most appropriate management at this time?

A. MRI of the ankle to evaluate for ligament tear
B. Referral to orthopedic surgeon
C. Repeat the plain x-rays
D. Increase her dose of ibuprofen
E. Refer her for physical therapy

ANSWERS

12.1 **C.** The Ottawa Ankle Rules apply in adult patients who have a normal mental status, who don't have other painful injuries, and who are seen within 10 days of their injury. The only setting in which all of these criteria apply is C.

12.2 **A.** Plain film x-rays are the diagnostic imaging test of choice for the initial evaluation of the painful joint. In patients who have normal x-rays and who have a suspected soft-tissue (ligament, tendon, cartilage) injury, MRI scanning is usually the next most appropriate imaging study to perform.

12.3 **E.** The most common cause of a stiff or painful joint following a sprain is inadequate rehabilitation. When a patient is unable to adequately self-rehabilitate an injury, a physical therapy referral can be beneficial. If the patient continues to have symptoms after that, consideration of advanced imaging or orthopedic referral is appropriate.

Clinical Pearls

- A complete history and physical is essential in diagnosing and treating musculoskeletal injuries.
- If you suspect that a patient's limited active range of motion is primarily a result of pain, you can numb the joint by injecting lidocaine into it and then reexamine the joint.
- Use the uninjured, contralateral extremity as a comparison for your examination of an injured extremity.
- An adequate x-ray series must include at least two views at 90° to each other.

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Case 13

A 45-year-old white woman presents to your office concerned about a "mole" on her face. She says that it has been present for years but her husband has been urging her to have it checked. She denies any pain, itching, or bleeding from the site. She has no significant past medical history, takes no medications, and has no allergies. She has no history of skin cancer in her family. She is an accountant by occupation.

On examination, the patient is normotensive, afebrile, and appears slightly younger than her stated age. A skin examination reveals a nontender, symmetric, 4-mm papule that is uniformly reddish-brown in color. The lesion is well circumscribed, and the surrounding skin is normal in appearance. There are no other lesions in the area.

- What is the most likely diagnosis?
- What features are reassuring of a benign condition?
- What is your next step?

ANSWERS TO CASE 13:
Skin Lesions

Summary: A 45-year-old healthy woman with no significant past medical history presents for evaluation of a skin lesion. She does not have a family history of skin cancer. The lesion is symmetric, with well-defined borders, relatively small (<6 mm), and uniform coloration. She is not able to assess whether the lesion has changed recently (ie, become larger), and does not give a history of itching or bleeding at the site of the lesion.

- **Most likely diagnosis:** Benign nevus.
- **Reassuring features:** Size less than 6 mm, symmetric, uniform color, well-defined borders.
- **Next step in treatment:** Reassurance and surveillance.

ANALYSIS

Objectives

1. Describe an approach to the evaluation of skin lesions.
2. Be able to describe the features of a skin lesion in dermatologic terms.
3. Know which features of a lesion are typically benign and which are concerning for malignancy or potential malignancy.

Considerations

This case represents a typical scenario seen in primary care medicine: "I have this mole. Is it cancer?" Although simplified, this is what the patient is most concerned about and wants to know. The **role of the physician is to determine the likelihood of malignancy or premalignancy and to define a course of action that is appropriate.** In this particular case, there are several features that reassure a benign condition that can be monitored without the need for a biopsy. There was neither a family medical history of skin cancer nor history of skin cancer in the patient. She has an occupation that does not expose her to harmful chemicals or the sun on a regular basis. On examination, the lesion has typically benign features (size <6 mm, symmetric, uniform color, well-defined borders). In this case, it would be appropriate to make a note (or possibly even a photograph) in the patient's chart describing the characteristic features of the lesion and monitor for changes in the lesion at periodic health evaluations. The patient should also be educated in self-examination of the skin, with an emphasis on what to look for and when to come to the physician's office for an evaluation of a new or changing skin lesion. Finally, it

should be understood that many otherwise benign-appearing moles might have an atypical characteristic that warrants further investigation. The **criteria that are used to predict the likelihood of a benign versus malignant lesion are only guidelines;** to be sure, not all malignant skin lesions present in the same manner and a malignant melanoma is not always visibly pigmented. The bottom line is that the physician should use all of the tools at his disposal: the history of present illness (HPI), medical history of the patient, the family medical history (FMH), social and occupational history, and a pertinent review of systems so as to arrive at a conclusion that is consistent with the physical examination.

APPROACH TO Skin Lesions

DEFINITIONS

ABSCESS: A closed pocket containing pus.

BULLA: A blister greater than 0.5 cm in diameter (plural: bullae).

CYST: A closed, saclike, membranous capsule containing a liquid or semisolid material.

MACULE: A discoloration on the skin that is neither raised nor depressed.

NODULE: A small mass of rounded or irregular shape that is greater than 1.0 cm in diameter.

PAPULE: A small, circumscribed *elevated* lesion of the skin that is less than 0.5 cm in diameter.

PLAQUE: A plateaulike, raised, solid area on the skin that covers a large surface area in relation to its height above the skin.

ULCER: A lesion through the skin or mucous membrane resulting from loss of tissue.

VESICLE: A small blister less than 0.5 cm in diameter.

CLINICAL APPROACH

Incidence and Risk Factors

There has been an increase in the morbidity and mortality of skin cancer in the past few decades in the United States. In 2007, nearly 60,000 new cases of melanoma were diagnosed. When you include basal cell carcinoma or squamous cell carcinoma, more than 1 million new cases of skin cancer are diagnosed annually. Skin cancers cause approximately 10,000 deaths per year, of which 80% are due to melanoma.

The **single most important risk factor for the development of skin cancer is exposure to ultraviolet radiation.** Other risk factors include a prior history of skin cancer, a family history of skin cancer, fair skin, red or blonde hair, a propensity to burn easily, chronic exposure to toxic compounds such as creosote, arsenic, or radium, and a suppressed immune system.

FOUR BASIC TYPES OF MELANOMA

Superficial Spreading Melanoma

This is the **most common type of melanoma** in both sexes. As its name implies, this lesion spreads superficially along the top layers of skin before penetrating into the deep layers. The superficial, or radial, growth phase is slower than the vertical phase, which is when the lesion grows into the dermis and can invade other tissues or metastasize. Men are more commonly affected on the upper torso, whereas women are affected mostly on the legs.

Lentigo Maligna

Similar to the superficial spreading type, this lesion is **most often found in the elderly,** usually on chronic sun-damaged skin such as the face, ears, arms, and upper trunk. Although it is the **least common of the four types of melanoma,** this is the most common form of melanoma found in Hawaii.

Acral Lentiginous Melanoma

Similar to the other two superficial melanomas in that it begins in situ, this lesion is different in many ways. This is the **most common melanoma found in African Americans and Asians.** This melanoma is usually found under the nails, on the soles of the feet, and on the palms of the hands.

Nodular Melanoma

This melanoma, unlike the other three, is usually invasive at the time of diagnosis. This is the **most aggressive type of melanoma (Figure 13–1).**

PHYSICAL EXAMINATION

In 1985, it was noted by clinicians studying melanoma that there were several characteristic features of skin lesions that correlated with melanoma. Specifically, color variegation, border irregularity, asymmetry, and size greater than 6 mm in diameter were consistently observed with melanoma. This led to the **ABCD acronym** which has been used extensively to determine the likelihood of a cancerous skin lesion (Table 13–1).

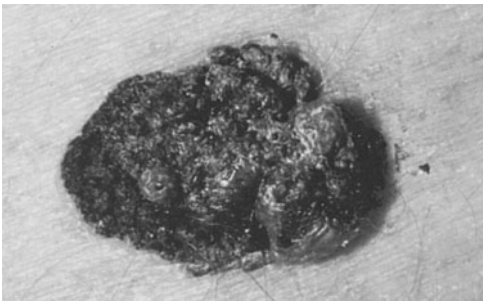

Figure 13–1. Nodular melanoma. *Reproduced with permission from Kasper DL, Braunwald E, Fauci A, et al.* Harrison's Principles of Internal Medicine. *16th ed. New York, NY: McGraw-Hill; 2005:499.*

One other criterion that is often used is the change in the size or appearance of the skin lesion. This is sometimes cited as E in the above ABCD criteria, and referred to as **E**volving. Benign lesions may present at birth, or any time thereafter, and several benign lesions may also present near the same point in time. However, a benign lesion, once present, will usually remain stable in size and appearance, whereas a malignancy will present as increasing in size or changing in appearance. Thus, it is useful to ask whether a "mole" has recently changed in appearance or has grown in size.

TREATMENT

Benign nevi need only be monitored visually. The patient can accomplish this after education on what to look for and when to come back for reevaluation. In general, any preexisting nevus that has changed or any new pigmented

Table 13–1 CLASSIC ABCD CRITERIA OF SUSPICIOUS SKIN LESIONS

ACRONYM	CHARACTERISTIC	MORE LIKELY BENIGN	MORE LIKELY MALIGNANT
A	Asymmetry	Symmetric (right half looks like left half)	Asymmetric
B	Borders	Well defined	Ragged or blurred
C	Color	Uniform color	Variegated
D	Diameter	Less than 6 mm	Greater than 6 mm
E	Elevation	Flat surface	Raised surface

lesion that exhibits any of the ABCDE signs should be excised completely with a 2- to 3-mm margin around the lesion. Larger lesions that may be cosmetically difficult to completely excise may be biopsied in several areas. If the pathology indicates a malignancy, the lesion should then be completely excised with 5-mm margins by a physician trained in plastic surgical technique. Complete excision of malignant melanomas requires at least a 5-mm margin. Once a patient has been identified as having a malignant skin lesion, the patient should be observed on an annual basis for any new or changing skin lesions. Shave biopsy may be used for raised lesions, and punch biopsy or elliptical excision for flat lesions. If the entire lesion cannot be removed due to size or location, biopsies should be taken from the most suspicious parts of the lesion.

PROGNOSIS

The single most important piece of information for prognosis in melanoma is the thickness of the tumor, known as the Breslow measurement. **Melanomas less than 1-mm thick have a low rate of metastasis** and a high cure rate with excision. Thicker melanomas have higher rates of metastases and poorer outcomes.

PREVENTION

Prevention is aimed at reducing exposure to ultraviolet radiation. When possible, avoid the sun between 10 AM and 4 PM; wear sun-protective clothing when exposed to sunlight; wear a sunscreen with a sun protection factor (SPF) of at least 15; and avoid artificial sources of ultraviolet (UV) radiation.

NONMELANOMA SKIN CANCERS

Both basal cell and squamous cell carcinomas arise from the epidermal layer of the skin. The primary risk for these types of skin cancers is exposure to ultraviolet radiation, especially sun exposure but also tanning bed use. A history of actinic keratoses and human papillomavirus infection of the skin also raises the risk of squamous cell carcinomas.

Basal cell carcinomas are the most common of all cancers. They typically appear as pearly papules, often with a central ulceration or with multiple telangiectasias. Patients typically present with a growing lesion and sometimes complain that it bleeds or itches. Basal cell carcinomas rarely metastasize but can grow large and can be locally destructive. The primary treatment is excision.

Squamous cell carcinomas have a higher rate of metastasis than basal cell carcinomas, but the risk is still low. These lesions are often irregularly shaped plaques or nodules with raised borders. They are frequently scaly, ulcerated, and bleed easily. Complete excision is the treatment of choice.

Comprehension Questions

13.1 A 36-year-old man is noted to have a bothersome "mole" that on biopsy reveals malignant melanoma. The pathologist comments that this histology is the most common type of melanoma in both males and females and has two growth phases. Which of the following is the most likely finding?

A. Benign nevus
B. Superficial spreading melanoma
C. Lentigo maligna
D. Nodular melanoma
E. Acral lentiginous melanoma

13.2 A 49-year-old fair skinned woman is noted to have a lesion on her right upper back that seems to have grown over the past year. It is noted to be 8 mm in diameter. The physician obtains an excisional biopsy, and it returns as malignant melanoma with invasion. Which of the following is the most likely finding on the biopsy?

A. Benign nevus
B. Superficial spreading melanoma
C. Lentigo maligna
D. Nodular melanoma
E. Acral lentiginous melanoma

13.3 A 54-year-old African-American man is noted to have a dark "spot" on his palm of his hand that his wife has noticed has become irregular in shape. On biopsy, it is a malignant melanoma. Which of the following is the most likely histology in this patient?

A. Benign nevus
B. Superficial spreading melanoma
C. Lentigo maligna
D. Nodular melanoma
E. Acral lentiginous melanoma

13.4 A 45-year-old African-American woman presents for a routine examination. You notice a 9-mm diameter lesion on the palm of her right hand that is dark black, slightly raised and has a notched border. When asked about it, she says that it has been present for about a year and is growing. A friend told her not to be concerned because, "black people don't get skin cancer." Which of the following is your advice?

A. Her friend is correct and this is nothing to worry about.
B. While anyone can get skin cancer, this lesion has primarily benign features and can be safely observed.
C. This lesion is suspicious for cancer but this most likely a metastasis from another source, such as a breast cancer.
D. This lesion is suspicious for a primary melanoma and needs further evaluation immediately.

13.5 A 70-year-old woman presents for evaluation of a lesion on her left cheek. It has been present for several months. It is slowly enlarging and bleeds if she scratches it. On examination, you find a 7 mm diameter pearly appearing papule with visible telangiectasias on the surface. Which of the following is the appropriate management of this lesion?

A. Close observation and reexamination in 3 months
B. Reassurance of the benign nature of the lesion
C. Excision
D. Local destruction by freezing with liquid nitrogen

ANSWERS

13.1 **B.** Superficial spreading melanomas are the most commonly occurring melanomas in both men and women.

13.2 **D.** Nodular melanomas are the most aggressive melanomas and are usually invasive at the time of diagnosis. This patient's lesion has grown quickly and is invasive.

13.3 **E.** Acral lentiginous melanomas are found on the palms of hands, soles of feet, and under finger- and toenails, and are the most common type found in African Americans and Asians.

13.4 **D.** The lesion described is suspicious for an acral lentiginous melanoma and needs evaluation. While skin cancers are more common in persons with lighter skin, they can occur in persons with any skin color or tone.

13.5 **C.** The lesion is most likely a basal cell carcinoma and should be treated with excision. While the likelihood of metastatic spread is low, these lesions can grow and be locally destructive.

Clinical Pearls

- The preventable risk factor common to all skin cancers is sun exposure. Recommend to your at-risk patients limiting exposure to sunlight in the middle of the day, wearing appropriate protective clothing, and using sun screen.
- Contrary to popular belief, the use of tanning beds is also a risk factor for skin cancer.
- There is no such thing as a "healthy tan."
- Excisional biopsy should be done for any lesion suspicious for melanoma. If the entire lesion cannot be removed due to size or location, full-thickness biopsies should be taken from the most suspicious parts of the lesion."

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Case 14

A 40-year-old male with no past medical history presents to the clinic to establish care. He reports that he had a prior urinalysis that revealed blood as an incidental finding. The urinalysis was done as a standard screening test by his former employer. He denies ever seeing any blood in his urine and denies any voiding difficulties, dysuria, sexual dysfunction, or any history or risk factors for sexually transmitted diseases. His review of systems is otherwise negative. He has smoked a half-pack of cigarettes per day for the past 10 years and exercises by jogging 15 minutes and light weight training daily. On examination, his vital signs are normal and the entire physical examination is unremarkable. A complete blood count (CBC) and a chemistry panel (electrolytes, blood urea nitrogen, and creatinine) are normal. The results of a urinalysis done in your office are: specific gravity, 1.015; pH 5.5; leukocyte esterase, negative; nitrites, negative; white blood cell count (WBC), 0; red blood cell count (RBC), 4 to 5 per high-power field (HPF).

- What is your diagnosis?
- How would you approach this patient?
- What is the workup and plan for this patient?
- What are the concerns and how would you counsel the patient?

ANSWERS TO CASE 14:
Hematuria

Summary: A 40-year-old male smoker is found incidentally to have red blood cells in his urine sample on a urinalysis.

- **Current diagnosis:** Asymptomatic microscopic hematuria.
- **Initial approach:** Repeat the urinalysis, assess for risk factors, image the upper and lower urinary tract.
- **Workup and plan:** Rule out infection by performing a urine culture; evaluate for malignancy by imaging of the upper urinary tract, cystoscopy, and voided cytology.
- **Concerns and counseling:** The primary concern is to rule out malignancy, including renal cell carcinoma and transitional cell carcinoma. Counsel the patient on the importance of an appropriate workup, but reassure the patient about the low prevalence of the condition.

ANALYSIS

Objectives

1. Learn about the significance of microscopic hematuria.
2. Learn an evidence-based approach to workup asymptomatic microscopic hematuria.
3. Be familiar with recommendations for follow-up on patients with hematuria after a negative workup.

Considerations

This patient has asymptomatic microscopic hematuria, as opposed to gross hematuria. Although he is asymptomatic, this patient deserves a thorough workup in order to determine an etiology, if possible, and to rule out malignancy.

The patient's history should be reviewed with specific questions to determine any risks for sexually transmitted diseases (STDs), occupational exposures to chemicals, strenuous exercise, drugs, medications, and herbal/nutritional supplements. The workup should begin with a repeat urinalysis. If the condition persists, the patient should have imaging studies of both the upper and lower urinary tract. The **upper tract can be imaged by either an intravenous pyelogram (IVP) or computed tomography (CT) scan**. The **lower tract is most commonly evaluated by cystoscopy,** an endoscopic procedure. Urine should also be sent for cytology and culture. Urologic consultation should be requested if the

workup reveals an abnormality that cannot be treated in a primary care office or if the condition persists. Inform the patient that a complete workup is necessary to evaluate for the presence of conditions such as infections or tumors, but he should be reassured that the **incidence of cancer presenting as asymptomatic microscopic hematuria is low.**

APPROACH TO Hematuria

DEFINITIONS

GROSS HEMATURIA: The presence of enough blood in a urine sample to be visible to the naked eye.

LOWER URINARY TRACT: The urinary bladder and urethra.

MICROSCOPIC HEMATURIA: The presence of 3 or more red blood cells per HPF on two or more properly collected urinalyses.

UPPER URINARY TRACT: The kidneys and ureters.

CLINICAL APPROACH

Hematuria is divided into glomerular, renal (nonglomerular), and urologic etiologies. Glomerular hematuria typically is associated with significant proteinuria, erythrocyte casts, and dysmorphic RBCs. Renal (nonglomerular) hematuria is secondary to tubulointerstitial, renovascular, and metabolic disorders. Like glomerular hematuria, it often is associated with significant proteinuria; however, there are no associated dysmorphic RBCs or erythrocyte casts. Urologic causes of hematuria include tumors, calculi, infections, trauma, and benign prostatic hyperplasia (BPH). Urologic hematuria is distinguished from other etiologies by the absence of proteinuria, dysmorphic RBCs, and erythrocyte casts.

Hematuria in adults should first be defined as gross hematuria or microscopic hematuria. Gross hematuria denotes that the patient is able to visualize blood in his voided specimen. Patients most often describe their urine as having a reddish or brownish color. They commonly are concerned about malignancy or kidney stones. In contrast, microscopic hematuria is usually asymptomatic and often discovered incidentally. Although a thorough workup of microscopic hematuria is advocated, many **authorities do not recommend routine screening for hematuria.**

Clinically significant microscopic hematuria is defined as 3 or more red blood cells per high-power field on microscopic evaluation of urinary sediment from two of three properly collected urinalysis specimens. The initial

determination of microscopic hematuria should be based on microscopic examination of urinary sediment from a freshly voided, early morning, clean-catch, midstream urine specimen. Urine must be refrigerated if it cannot be examined promptly, as delays of more than 2 hours between collection and examination often cause unreliable results.

Hematuria can be measured quantitatively by any of the following methods:

- Determination of the number of red blood cells per milliliter of urine excreted (chamber count)
- Direct examination of the centrifuged urinary sediment (sediment count)
- Indirect examination of the urine by dipstick (the simplest way to detect microscopic hematuria).

Given the limited specificity of the dipstick method (65%-99% for 2-5 red blood cells per high-power microscopic field) however, the initial **finding of hematuria by the dipstick method should be confirmed by microscopic evaluation of urinary sediment.** The limited specificity is due to the fact that the urine dipstick lacks the ability to distinguish red blood cells from myoglobin or hemoglobin.

Despite the recommendation that two positive urinalyses are needed prior to workup, it is important to consider the individual patient's risk factors. If a patient has significant risk factors, even one properly collected urine specimen with 1 to 2 RBCs is sufficient to warrant a workup. Risk factors include smoking, occupational exposure to chemicals or dyes (benzenes or aromatic amines), history of gross hematuria, older than age 40 years, history of urologic disorder or disease, history of irritative voiding symptoms, history of urinary tract infection, analgesic abuse, or history of pelvic irradiation.

The prevalence of asymptomatic hematuria is roughly 0.20% in the adult population in the United States. There are myriad possible causes; risk factors should guide the specific workup for the individual patient. Although some elements of the workup are standard for everyone, other more detailed and expensive tests can be deferred for those at low risk. The presence of significant proteinuria, red cell casts, or renal insufficiency, or a predominance of dysmorphic red blood cells in the urine should prompt an evaluation for renal parenchymal disease or referral to a nephrologist. In general, glomerular bleeding is associated with more than 80% dysmorphic red blood cells, whereas lower urinary tract bleeding is associated with more than 80% normal red blood cells.

Evaluation

Evaluation of the **urinary sediment** can allow for the diagnosis of patients with renal parenchymal disease. This analysis **will often also allow for distinction between glomerular disease and interstitial nephritis.** The presence of red cell casts and dysmorphic red blood cells is suggestive of renal glomerular disease. Interstitial nephritis, often caused by analgesics or other drugs, is suggested by the presence of eosinophils in the urine.

A complete evaluation for microscopic hematuria starts with a detailed history and physical examination, appropriate laboratory testing (including urinary cytology), and imaging of the upper and lower urinary tract. In all patients, the urinalysis should be repeated. If the repeat urinalysis is negative and the patient remains asymptomatic, no further workup is required for low-risk patients. Transient microscopic hematuria can be caused by sexual intercourse, heavy exercise, a recent digital prostate examination, or contamination by menses. However, if the hematuria persists, a full workup is warranted regardless of a benign history or physical examination. The repeat urinalysis should be done after avoidance of any potential confounders such as menses, medications, exercise, drugs, and nutritional/herbal products. Exercise-induced hematuria usually resolves spontaneously in 72 hours in the absence of other coexisting conditions. In addition, careful attention should be taken in women to ensure the blood is not from the vaginal or rectal areas. In men, one should also exclude local trauma to the foreskin. If in doubt, a catheterized specimen should be obtained, taking care not to induce trauma during the procedure.

The laboratory studies should start with urinalysis with microscopy and evaluation of centrifuged urinary sediment. The urine should be examined for number of RBCs per high-power field, dysmorphic RBCs, and presence of casts and eosinophils. Urinary tract infection (UTI) should be ruled out by urine culture. If an infection is present, it should be appropriately treated and the urinalysis repeated in 6 weeks. If the **hematuria resolves with treatment of the UTI, no further workup is needed.**

A serum creatinine should also be obtained to assess renal function, with comparison to old records if available. If the laboratory evaluation reveals elevated creatinine or red cell casts, workup should focus on renal parenchymal disease and possible etiologies such as hypertension, diabetes, or autoimmune diseases. Renal biopsy may be appropriate for certain individuals. Patients with risk factors should also undergo cytologic evaluation of the urine to assess for transitional cell carcinoma. Although voided urine cytology may not pick up low-grade carcinoma, it is fairly reliable for high-grade lesions, especially if repeated.

Numerous options exist for imaging of the upper urinary tract. Despite many studies comparing the radiographic methods, there are no evidence-based guidelines on which modality is most efficient. An IVP is x-ray imaging of the upper urinary tract after the administration of an intravenous contrast dye. It is a widely available and relatively low-cost procedure, but it can miss small renal masses and may not distinguish solid from cystic lesions. Ultrasonography is also widely available and does not require the use of contrast dye but also may miss small lesions. CT scanning has a high sensitivity and specificity for detecting masses, renal stones, renal or perirenal infections, and obstruction. The CT scan should be initially performed as a noncontrast study to detect calculi, and then a contrast study should be obtained. Both CT scanning and IVP may lead to nephropathy caused by IV contrast dye. Premedication with *N*-acetylcysteine or IV sodium bicarbonate may be used to reduce the risk contrast nephropathy. In patients with renal insufficiency or who are at high risk of contrast nephropathy,

a retrograde pyelography combined with a renal ultrasound may be an option. Retrograde pyelography is an invasive procedure in which a catheter is placed in the bladder and dye injected up the ureters to the kidneys. There is little risk of contrast nephropathy because no contrast dye is given IV.

The lower urinary tract should be examined for transitional cell carcinoma by cystoscopy performed by an urologist. In the absence of risk factors in selected patients with a negative history, examination, laboratory workup, and upper tract imaging, cystoscopy may be deferred or individualized at the discretion of the treating physician.

In patients with a thorough but negative workup, the American Urological Association recommends follow-up blood pressure measurements, urinalyses, and voided urine cytologic studies at 6, 12, 24, and 36 months. The reason for the regular follow-up is to assess for the possibility of an underlying lesion, despite a low likelihood of there being one. If the workup remains negative for 36 months and the patient continues to be asymptomatic, no further follow-up is recommended. However, if the patient develops gross hematuria, voiding difficulties, pain, or any abnormal cytology, immediate urologic reevaluation and urologic consultation is warranted. Patients who develop hypertension, proteinuria, glomerular casts, or abnormal renal function should be referred to a nephrologist for consultation.

Comprehension Questions

14.1 A 24-year-old male bodybuilder with no significant medical history presents with gross hematuria. He was told by his trainer that exercise can induce hematuria and that this is nothing to worry about. He comes to you for a second opinion. Which of the following is the most appropriate management at this time?

A. Urinalysis now. If no blood is noted, repeat in 6 months.
B. Urinalysis and urine culture now. If they are normal, no other workup is needed.
C. Urinalysis after 72-hours of no exercise. If no blood in urine then, diagnose exercise-induced hematuria.
D. Urinalysis, urine culture, and imaging of upper urinary tract by CT scanning.

14.2 A 78-year-old man with multiple medical problems presents with dysuria and is found to have microscopic hematuria. His examination is only positive for a very tender and boggy prostate. Which of the following is the best next step?

A. Stat urology referral.
B. Treat the prostatitis with 1 month of antibiotics and reevaluate the patient with a follow-up urinalysis and culture posttreatment.
C. Obtain an IVP followed by cystoscopy.
D. Obtain a CT of the abdomen and pelvis, followed by cystoscopy.

14.3 A 45-year-old woman with a history of cancer, currently receiving radiation therapy, presents as a new patient. On a routine urinalysis, you discover 2 RBCs per HPF, 15 to 20 WBCs per HPF, nitrites, and leukocyte esterase. Which of the following is the next most appropriate step?

A. Repeat a clean-catch midstream specimen, send for culture, and treat the UTI. Repeat urinalysis after the UTI treatment.
B. Treat the UTI and also refer the patient for an IVP and cystoscopy.
C. Check urine for cytology.
D. Inform the patient that the urinalysis results are a result of the radiation treatment and no further workup is needed.

ANSWERS

14.1 **D.** Gross hematuria always deserves a full workup. Although exercise-induced hematuria resolves in 72 hours, gross hematuria, especially in a person with risk factors, must have a thorough evaluation.

14.2 **B.** A tender/boggy prostate alludes to the diagnosis of prostatitis. Reevaluation should be done after adequate treatment of the prostatitis. If the hematuria persists following treatment, further workup is necessary.

14.3 **A.** True microscopic hematuria is the presence of 3 or more RBCs per HPF in a midstream clean-catch specimen after exclusion of a UTI. If there is evidence of a UTI, it should be cultured, treated, and urinalysis repeated after treatment.

Clinical Pearls

- Hematuria in adults always should be evaluated. If no source is found on a thorough initial workup, patients should be followed for at least 3 years to monitor for an underlying condition.
- Patients should be thoroughly instructed in the proper technique for a "clean-catch" urine sample. This will reduce the number of false-positive findings.

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Case 15

A 27-year-old woman presents to your office complaining of progressing nervousness, fatigue, palpitations, and the recent development of a resting hand tremor. She also states that she is having difficulty concentrating at work and has been more irritable with her coworkers. The patient also notes that she has developed a persistent rash over her shins that has not improved with the use of topical steroid creams. All of her symptoms have come on gradually over the past few months and continue to get worse. Review of systems also reveals an unintentional weight loss of about 10 lb, insomnia, and amenorrhea for the past 2 months (the patient's menstrual cycles are usually quite regular). The patient's past medical history is unremarkable and she takes no oral medications. She is currently not sexually active and does not drink alcohol, smoke, or use any illicit drugs. On examination, she is afebrile. Her pulse varies from 70 to 110 beats/min. She appears restless and anxious. Her skin is warm and moist. Her eyes show evidence of exophthalmos and lid retraction bilaterally, although funduscopic examination is normal. Neck examination reveals symmetric thyroid enlargement, without any discrete palpable masses. Cardiac examination reveals an irregular rhythm. Her lungs are clear to auscultation. Extremity examination reveals an erythematous, thickened rash on both shins. Neurologic examination is normal except for a fine resting tremor in her hands when she attempts to hold out her outstretched arms. Initial lab tests include a negative pregnancy test and an undetectable level of thyroid-stimulating hormone (TSH).

- What is the most likely diagnosis?
- What imaging study is most appropriate at this time?
- What is the definitive nonsurgical treatment of this condition?

ANSWERS TO CASE 15:
Thyroid Disorders

Summary: A 27-year-old female with progressively worsening anxiety, palpitations, tremor, menstrual irregularities, and weight loss. Her TSH level is suppressed, confirming the presence of hyperthyroidism.

- **Most likely diagnosis:** Hyperthyroidism secondary to Graves disease
- **Most appropriate imaging study:** Nuclear medicine thyroid scan with uptake
- **Definitive nonsurgical treatment:** Thyroid ablation with radioactive iodine

ANALYSIS

Objectives

1. Know the most common conditions that cause hyper- and hypothyroidism.
2. Be able to interpret the common tests used to evaluate thyroid function.
3. Learn the modalities of treatment for disorders of the thyroid.

Considerations

This patient has symptoms and signs consistent with hyperthyroidism, including warm, moist skin caused by excessive sweating and cutaneous vasodilation; a resting tremor; an enlarged thyroid gland; weight loss; and tachycardia. Her irregular heart beat may be a manifestation of atrial fibrillation, which occurs in approximately 10% of hyperthyroid patients. Eye abnormalities are common in hyperthyroid states. Retraction of the upper lid, resulting in the "thyroid stare" is common. Graves disease has a unique ophthalmopathy that may cause a prominent exophthalmos **(Figure 15–1). The most common cause of noniatrogenic hyperthyroidism is Graves disease,** an autoimmune thyroid disorder. Autoantibodies to the TSH receptors on the thyroid gland result in hyperfunctioning of the gland, with the result that the thyroid gland functions outside the usual control of the hypothalamic-pituitary axis. Graves disease commonly occurs in reproductive-age females and is much more common in women than men. The treatment of Graves disease includes antithyroid drugs (such as propylthiouracil and methimazole) and/or β-blockers to block some of the peripheral effects of the excessive thyroxine. However, these are only temporary measures used to give patients symptomatic relief. The definitive treatment is radioactive iodine, which destroys the thyroid gland. **At least 40% of patients who receive radioactive iodine eventually become hypothyroid** and will need thyroid hormone replacement. Radioactive

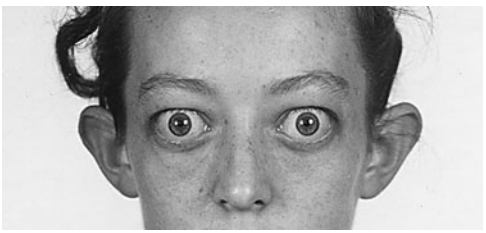

Figure 15–1. Exophthalmos and proptosis of Graves disease. *Reproduced with permission from Kasper DL, Braunwald E, Fauci A, et al.* Harrison's Principles of Internal Medicine, *16th ed. New York, NY: McGraw-Hill; 2005:2114.*

iodine therapy is contraindicated in pregnant women, as the isotope can cross the placenta and cause fetal thyroid ablation. Surgical removal of the thyroid gland is another option for the treatment of Graves disease, but it is often reserved for pregnant patients.

APPROACH TO Thyroid Disease

DEFINITIONS

GRAVES DISEASE: An autoimmune thyroid disorder in which autoantibodies to the TSH receptors on the thyroid gland result in hyperfunctioning of the thyroid gland. A prominent finding is also the "stare" due to the ophthalmic involvement.

THYROID STORM: An acute hypermetabolic state associated with the sudden release of large amounts of thyroid hormone into circulation, leading to autonomic instability and central nervous system dysfunction such as altered mental status, coma, or seizures. This condition has a significant mortality risk.

HYPERTHYROIDISM

Signs and Symptoms

Hyperthyroidism usually presents with progressing nervousness, palpitations, weight loss, fine resting tremor, dyspnea on exertion, and difficulty with concentration. Physical findings include a rapid pulse rate and elevated blood

pressure, with the systolic pressure increased to a greater extent than the diastolic pressure, creating a widened pulse-pressure hypertension. Examination findings can include atrial fibrillation and a fine resting tremor.

Thyroid storm is an acute hypermetabolic state associated with the sudden release of large amounts of thyroid hormone into circulation. It occurs most often in patients with Graves disease, but can also occur in acute thyroiditis conditions. Symptoms include fever, confusion, restlessness, and psychoticlike behavior. Examination may demonstrate tachycardia, elevated blood pressure, fever, and dysrhythmias. Patients can also have other signs of high-output heart failure, such as dyspnea on exertion and peripheral vasoconstriction, and may exhibit signs of cerebral or cardiac ischemia. **Thyroid storm is a medical emergency** that requires prompt attention and reversal of the metabolic demands of the acute hyperthyroidism.

Pathogenesis

Graves disease is the most common cause of hyperthyroidism and is more commonly found in women. It is an autoimmune disorder caused by immunoglobulin (Ig) G antibodies that bind to TSH receptors, initiating the production and release of thyroid hormone. In addition to the usual findings, approximately **50% of patients with Graves disease also have exophthalmos.** The second most common cause of hyperthyroidism is an autonomous thyroid nodule that secretes thyroxine. These nodules do not rely on TSH stimulation and continue to excrete large amounts of thyroxine despite low, or nonexistent, circulating TSH levels. Hyperthyroidism can also be caused by the acute release of thyroid hormone in the early stages of thyroiditis. In such cases, symptoms are generally transient and resolve within weeks of onset. Iatrogenic hyperthyroidism can occur secondary to the overuse of thyroxine supplementation.

Laboratory and Imaging Evaluation

Hyperthyroidism can be diagnosed by an elevated free thyroxine level, usually with a corresponding low TSH level. Once it has been identified, further testing for autoimmune antibodies and radionucleotide scanning of the thyroid can help to determine whether the problem is Graves disease, an autonomous nodule, or thyroiditis. Radionucleotide imaging provides a direct scan of the gland and an indication of its functioning. Imaging is performed using either an isotope of technetium-99 m (^{99m}Tc) or iodine-123 (^{123}I). After the administration of one of these agents, imaging the thyroid allows visualization of active and inactive areas, as well as an indication as to the level of activity in a particular area. In patients with Graves disease, there will be diffuse hyperactivity with large amounts of uptake. In contrast, thyroiditis demonstrates patchy uptake with overall reduced activity, reflecting the release of existing hormone rather than the overproduction of new thyroxine. The detection of serum thyroid-receptor antibodies is a specific diagnostic test for Graves disease.

Treatment

Radioactive iodine is the treatment of choice for Graves disease in adult patients who are not pregnant. It should not be used in children or breast-feeding mothers. Antithyroid drugs are also well tolerated and successful at blocking the production and release of thyroid hormone in patients with Graves disease. Some examples of these drugs include propylthiouracil (PTU), methimazole, and carbimazole. These drugs work by inhibiting the organification of iodine, although PTU also prevents the peripheral conversion of thyroxine (T_4) to triiodothyronine (T_3), its more active form. The most serious potential side effect of these drugs is agranulocytosis, which occurs in 3 per 10,000 treated patients per year. All of these drugs are relatively safe during pregnancy, although PTU is the preferred agent. **Antithyroid drugs are especially useful in treating adolescents, in whom Graves disease may go into spontaneous remission after 6 to 18 months of therapy.** Surgery is reserved for patients in whom medications and radioactive iodine ablation are unacceptable treatment modalities, or in whom a large goiter is present that is either compressing nearby structures or is disfiguring. For patients presenting with thyroid storm, aggressive initial therapy is essential to prevent complications. Treatment should include the administration of high doses of PTU and β-blockers (to control tachycardia and other peripheral symptoms of thyrotoxicosis). Hydrocortisone is given to prevent possible adrenal crisis.

HYPOTHYROIDISM

Signs and Symptoms

Patients with hypothyroidism can present with a wide range of symptoms, including lethargy, weight gain, hair loss, dry skin, slowed mentation or forgetfulness, constipation, intolerance to cold, and a depressed affect. **In older patients, hypothyroidism can be confused with Alzheimer disease** and other conditions that cause dementia. In women, it is often confused with depression. Physical findings that can present in hypothyroid patients include low blood pressure, bradycardia, nonpitting edema, hair thinning or loss, dry skin, and a diminished relaxation phase of reflexes.

Pathogenesis

Several different conditions can cause hypothyroidism. The **most common noniatrogenic condition causing hypothyroidism in the United States is Hashimoto thyroiditis,** an autoimmune thyroiditis. Iatrogenic causes include post-Graves disease thyroid ablation and surgical removal of the thyroid gland. Another cause is secondary hypothyroidism related to hypothalamic or pituitary dysfunction. These conditions are primarily found in patients who have received intracranial irradiation or surgical removal of a pituitary adenoma.

Laboratory and Imaging Evaluation

In primary hypothyroidism, the TSH level is elevated, indicating insufficient thyroid hormone production to meet metabolic demands. Free thyroid levels are low. In contrast, patients with secondary hypothyroidism have low or undetectable TSH levels. **Once the diagnosis of primary hypothyroidism is made, further imaging or serologic testing is unnecessary if the thyroid gland is normal on physical examination.** In cases of secondary hypothyroidism, however, further testing is needed to determine whether the cause is a hypothalamic or pituitary problem. This can be done by using a thyroid-releasing hormone (TRH) test. Endogenous TRH is released by the hypothalamus and stimulates the pituitary to release TSH. When TRH is injected intravenously, a normally functioning pituitary will result in an increase of TSH that can be measured in about 30 minutes. No increase in TSH after injection of TRH suggests a malfunctioning pituitary gland. In cases where pituitary dysfunction is suspected, imaging of the pituitary gland to detect microadenomas and testing of other hormones that are dependent on pituitary stimulation are indicated.

Treatment

Most healthy adults with hypothyroidism require about 1.7 μg/kg of thyroid hormone replacement daily, with requirements falling to about 1 μg/kg for the elderly. This usually amounts to between 0.10 and 0.15 mg/d of levothyroxine. Children with hypothyroidism may require higher doses for full replacement. In young patients without cardiovascular risk factors, replacement can start close to the estimated daily requirement. Older patients or those with risks for cardiovascular compromise that could occur with a rapid increase in resting heart rate and blood pressure should be started on lower doses and gradually increased over time. Doses can be increased in increments of 0.025 to 0.050 mg every 4 to 6 weeks until TSH levels return to normal. Thyroxine is usually dosed once daily, although some evidence suggests that weekly dosing may also be effective. In patients with an intact hypothalamic-pituitary axis, the adequacy of thyroid replacement can be followed with serial TSH measurements. Evaluation of TSH levels should be performed no earlier than 4 weeks after an adjustment in medication has been made. Full effects of thyroid replacement on TSH level may not be present until after 8 weeks of treatment. With increased age, thyroid binding decreases as a consequence of a drop in serum albumin level and medication dosage may need to be reduced by up to 20%. Annual monitoring of the TSH level in the elderly is necessary to avoid overreplacement.

NODULAR THYROID DISEASE

Thyroid nodules, both solitary and multiple, are common and are often found incidentally on physical examination, ultrasonography, or computed tomography. They are more prevalent in women and increase in frequency with age.

Although their pathogenesis is not clear, nodules are known to be associated with iodine deficiency, higher gravidity, and the ingestion of goitrogens. **Further workup of identified nodules is indicated, as the incidence of malignancy in solitary nodules is estimated at 5% to 6%.** The incidence of malignancy is higher in children, adults younger than 30 or older than 60 years, and patients with a history of head or neck irradiation. Other historical risk factors include a family history of thyroid cancer, the presence of cervical lymphadenopathy, and the recent development of hoarseness of the voice, progressive dysphagia, or shortness of breath.

Initial assessment should include evaluation of thyroid function. **Functional adenomas that present with hyperthyroidism are rarely malignant.** These represent less than 10% of all nodules. These patients are best evaluated with a radioactive iodine uptake study to confirm functionality of the nodule. Hyperfunctioning nodules are treated with surgery or radioactive ablation therapy, depending on the level of hyperthyroidism.

Nonfunctioning nodules measuring greater than 1 cm by examination or ultrasonography require biopsy. This can be done by fine-needle aspiration (FNA), which is a highly sensitive test. Ultrasound findings suggestive of malignancy include irregular margins, intranodular vascular spots, and microcalcifications. Results of the FNA determine further management and treatment. Cytologic evaluation of FNA specimens are reported as being nondiagnostic, benign, indeterminate, or malignant. **Follicular cell malignancy cannot be distinguished cytologically from its benign equivalent,** and thus is often read as indeterminate. These patients should be referred to surgery to obtain a definitive evaluation. Papillary, medullary, and anaplastic thyroid carcinomas can be diagnosed accurately by FNA. Patients with thyroid malignancy are treated by thyroidectomy followed by radioactive ablation. These patients will require long-term follow-up by an endocrinologist.

Thyroid nodules discovered during pregnancy are handled similarly, except that radioisotope scanning is contraindicated. Fine-needle aspiration is safe during pregnancy, and thyroidectomy can be performed relatively safely during the second trimester. However, because thyroid cancer is relatively indolent, it may be wise to defer definitive diagnosis and treatment until the postpartum period in patients with indeterminate lesions on FNA.

Comprehension Questions

15.1 A 28-year-old woman is noted to have had 10 lb unintended weight loss, nervousness, palpitations, and tremor. She is diagnosed with probable hyperthyroidism. Which of the following laboratory test results is most consistent with hyperthyroidism?

A. Normal TSH and elevated T_4/T_3 levels
B. Elevated TSH levels and low T_4/T_3
C. Elevated TSH levels and normal T_4/T_3
D. Low TSH and elevated T_4/T_3 levels

15.2 A 35-year-old woman presents with increasing fatigue for several months. She has also gained 10 lb, despite a decrease in her appetite. Her past medical history is significant for Graves Disease, which was treated with radioactive iodine. Laboratory studies confirm that TSH is elevated. Which of the following is the best treatment for this patient?

A. Propylthiouracil (PTU)
B. β-blockers
C. Levothyroxine
D. Thyroidectomy

15.3 A 24-year-old woman who is 8 weeks pregnant is found to have a thyroid nodule. Biopsy is performed and malignancy of the thyroid is diagnosed. Which of the following management options is most appropriate?

A. Confirm the diagnosis of cancer using radioisotope scanning.
B. Perform an immediate thyroidectomy
C. Follow clinically until after delivery of child
D. Treat with radioactive iodine ablation in the second or third trimester.

15.4 A 28-year-old man presents to his physician for a health maintenance visit. He feels well and does not report changes in his appetite, weight, energy, or bowel movements. A firm nodule is palpated in the left lobe of his thyroid. The nodule is confirmed on ultrasound and measures 1.3 cm. Which of the following is the next step in the workup of this nodule?

A. Radioactive iodine uptake study
B. Fine needle aspiration
C. Repeat ultrasound in 6 months
D. Referral to surgeon for open biopsy

ANSWERS

15.1 **D.** Most cases of hyperthyroidism will result in a suppressed level of TSH and elevated T_4/T_3 levels. An exception to this would be a secondary hyperthyroid state, such as with a pituitary tumor that secretes TSH, resulting in both a high TSH level and high serum hormone levels (caused by overstimulation of the thyroid gland).

15.2 **C.** This patient most likely has hypothyroidism due to the prior radioactive iodide therapy for ablation of the thyroid gland. Most cases of hypothyroidism are treated with thyroxine given orally. T_4 given in pill form will convert to the more metabolically active T_3.

15.3 **C.** Thyroid cancer detected during pregnancy can usually be observed until after the pregnancy is complete. If needed, thyroid surgery can be performed safely in the second and third trimesters. The use of radioactive iodine is contraindicated in pregnancy.

15.4 **B.** Fine needle aspiration is a sensitive and specific test for thyroid nodules and can help to determine whether it is malignant.

Clinical Pearls

- The most common forms of both hyper- and hypothyroidism are autoimmune: Graves disease causing hyperthyroidism and Hashimoto thyroiditis causing hypothyroidism.
- Hyperfunctioning ("hot") thyroid nodules are rarely malignant. Hypofunctioning ("cold") nodules more than 1 cm in diameter should be biopsied.
- Thyroid disease is more common in women than men.

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Case 16

A 25-year-old G2 P1 woman at 39 weeks estimated gestational age presents to the labor and delivery triage unit stating that her "water has broken." She reports having had a large gush of clear fluid followed by a constant leakage of fluid from her vagina. She subsequently started having uterine contractions approximately every 4 minutes. She has had an uncomplicated prenatal course with good prenatal care since 8-week gestation. Her prenatal records are available for review in the triage unit. Her first pregnancy resulted in the full-term delivery of a 7 lb 8 oz, healthy boy.

In the triage unit, she is placed on an external fetal monitor. Her blood pressure is 110/70 mm Hg, her pulse is 90 beats/min, and her temperature is 98.7°F (37.0°C). Her general examination is normal. Her abdomen is gravid, with a fundal height of 38 cm. The fetus has a cephalic presentation by Leopold maneuvers and an estimated fetal weight of 8 lb.

- What signs and tests could confirm the presence of rupture of membranes?
- On the fetal monitoring strip shown (Figure 16–1), what is the approximate baseline fetal heart rate? How often is she having uterine contractions?
- Her prenatal records reveal that she had a positive group B *Streptococcus* (GBS) vaginal culture at 36-week gestation. What therapy should be instituted at this time?

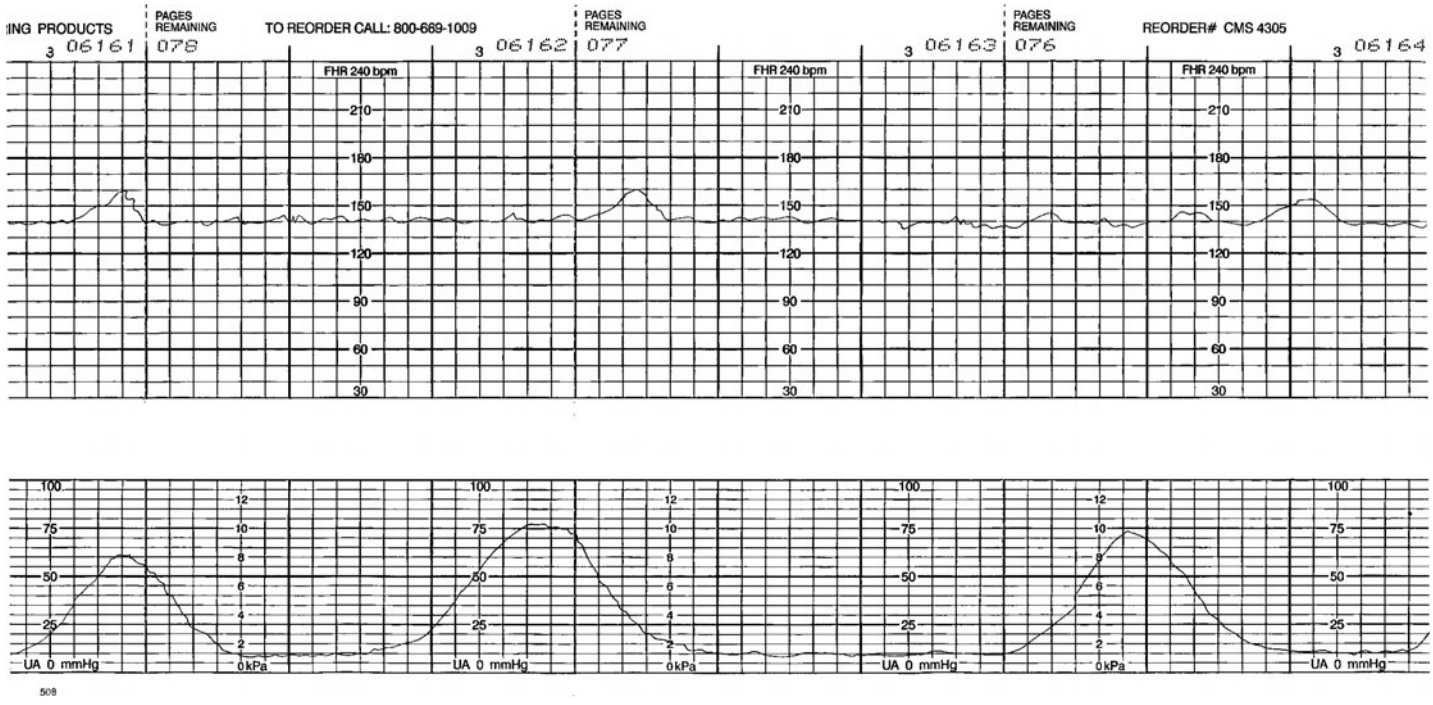

Figure 16–1. Fetal heart rate monitoring.

ANSWERS TO CASE 16:
Labor and Delivery

Summary: A 25-year-old pregnant woman at term presents with the spontaneous rupture of membranes and subsequent uterine contractions, signaling the onset of labor.

- **Signs that could confirm the rupture of membranes:** Visualization of amniotic fluid leaking from the cervix; the presence of pooling of amniotic fluid in the posterior vaginal fornix; demonstration of a pH above 6.5 in fluid collected from the vagina using Nitrazine paper; or visualization of "ferning" on a sample of fluid on an air-dried microscope slide
- **Baseline fetal heart rate:** 140 beats/min; **Contraction interval:** approximately every 3 minutes
- **Recommended antibiotic prophylaxis for GBS colonization during labor:** Penicillin 5 million units IV loading dose followed by 2.5 million units IV every 4 hours; alternative treatments include IV ampicillin, cephalothin, erythromycin, clindamycin, and vancomycin

ANALYSIS

Objectives

1. Know the definition of labor, including the three stages of labor, and know the normal progression of labor in nulliparous and multiparous women.
2. Understand the types of fetal monitoring that are routinely performed during labor and how monitoring correlates with the physiologic processes occurring during labor.
3. Be familiar with the abnormal progression of labor and some of the interventions that can be made to address these problems.

Considerations

This woman arrives at the labor and delivery triage unit in need of evaluation for the possibility that she is in labor and that she has ruptured her membranes (broken her bag of water). The accurate and appropriate diagnosis of labor is extremely important in obstetrical care. Incorrectly diagnosing a woman as being in labor may result in unnecessary interventions, whereas not diagnosing labor may result in complications or delivery occurring without access to appropriate personnel and facilities. Furthermore, the diagnosis of rupture of membranes is critical for several reasons. First, especially at term, the spontaneous rupture of membranes may signify the impending onset of labor. Second,

if the presenting part is not well applied in the pelvis, prolapse of the umbilical cord with resultant compression of the cord and disruption of the oxygen supply to the fetus may occur. Finally, the prolonged rupture of membranes, especially after 24 hours or longer, may predispose to the development of infection.

The physician also must promptly make assessments of both maternal and fetal well-being. A careful history and physical examination should be performed. When available, prenatal records should be reviewed to evaluate for any problems during this, or previous, pregnancies and to confirm the gestational age of the pregnancy. In this case, the presence of GBS colonization requires the institution of appropriate antibiotic prophylaxis to reduce the risk of fetal infection with GBS, a common cause of neonatal morbidity and mortality. In GBS-colonized women, the recommended antibiotic prophylaxis is IV penicillin. When this is not available, ampicillin is often substituted. In penicillin-allergic women, cephalothin, erythromycin, clindamycin, or vancomycin can be used. Fetal well-being is monitored most commonly using external, electronic fetal-monitoring equipment, although other options are available. With this equipment, the baseline fetal heart rate, heart rate variability, accelerations and decelerations, along with the presence and frequency of uterine contractions, may be evaluated. Determination of the presentation of the fetus (cephalic, breech, or shoulder [ie, transverse lie]) is also critical, as this may play a significant role in the determination of route of delivery (vaginal or cesarean).

APPROACH TO
Labor and Delivery

DEFINITIONS

FETAL LIE: The relationship of the long axis of the fetus to the long axis of the mother; either longitudinal or transverse.

FETAL PRESENTATION: The part of the fetus that is either foremost in the birth canal or in closest proximity to the birth canal.

LABOR: Regular uterine contractions that lead to the effacement and dilation of the cervix.

PREMATURE RUPTURE OF MEMBRANES: Rupture of the fetal membranes prior to the onset of labor.

CLINICAL APPROACH

Labor usually begins spontaneously and occurs normally within 2 weeks of the estimated date of confinement (280 days after the first day of the last menstrual period). The onset of labor more than 3 weeks before the estimated date of

confinement (EDC) is considered preterm labor. If labor has not started spontaneously by 2 weeks after the EDC, the pregnancy is considered postterm.

Stages of labor

Labor is typically divided into three stages. The **first stage of labor is from the onset of labor until the cervix is completely dilated.** This stage can further be divided into a latent phase and an active phase. During the latent phase of labor, the contractions become stronger, longer lasting, and more coordinated. The active phase of labor, which usually starts at 3 to 4 cm of cervical dilation, is when the rate of cervical dilation is at its maximum. Contractions are usually strong and regular. In active labor in a woman without an epidural, the minimum expected rates of cervical dilation are 1.2 cm per hour for a nulliparous woman and 1.5 cm per hour for a parous woman. The **second stage of labor is from complete cervical dilation (10 cm) through the delivery of the fetus.** The combination of the force of the uterine contractions and the pushing efforts of the mother results in the delivery of the baby. A normal second stage lasts less than 2 hours in a nulliparous patient and less than 1 hour in a parous patient. The presence of epidural anesthesia can prolong these times by up to 1 hour. The **third stage of labor begins after the delivery of the baby and ends with the delivery of the placenta and membranes.** The third stage is typically short and is considered prolonged if it lasts longer than 30 minutes.

The progress of labor

The progress of labor usually depends upon the **"three Ps."** The **Power** is the strength of the uterine contractions during the active phase of labor and of the maternal pushing efforts during the second stage of labor. The power of the contractions can be assessed subjectively by an examiner palpating the uterus during a contraction or objectively by placing an intrauterine pressure catheter, which directly measures pressure within the uterine cavity. The **Passenger** is the fetus. Its size, lie, presentation, and position within the birth canal all play a role in the progression of labor and rate of fetal descent. Finally, the shape and size of the **Pelvis** can result in delay or failure of descent of the fetus because of the relative disproportion between the fetal and pelvic sizes.

The diagnosis of active labor is an indication for admission to the birthing unit for labor management and monitoring. The presence of ruptured membranes is also an indication for admission. The rupture of membranes can be confirmed by a careful vaginal examination performed with a sterile speculum and gloves. The visualization of fluid leaking from the cervical os, either spontaneously or with the patient performing a Valsalva maneuver, and the presence of amniotic fluid pooling in the posterior vaginal fornix are confirmatory. The detection of fluid in the vagina with a pH more than 6.5 is consistent with amniotic fluid, as normal vaginal secretions typically have a pH less than 5.5. Using a sterile applicator to sample vaginal fluid and applying it to Nitrazine

paper can make this determination. The presence of semen, blood, or bacterial vaginosis can cause elevated pH in vaginal secretions and a false-positive Nitrazine test. The visualization of ferning of vaginal fluid under microscopic magnification of an air-dried sample also suggests the presence of amniotic fluid.

When the pregnant patient is admitted to the labor and delivery unit, **fetal well-being is assessed by either continuous or intermittent fetal heart rate monitoring.** Continuous external fetal heart rate monitoring is the more commonly used procedure in the United States. A Doppler ultrasound device is used to continuously trace the fetal heart rate. Continuous monitoring can also be accomplished using an internal device, by attaching an electrode to the fetal scalp that directly measures and amplifies fetal cardiac electrical activity. This procedure requires that the membranes are ruptured. With either of these two techniques, a continuous graphic recording of the fetal heart rate is recorded. Alternatively, intermittent auscultation using a stethoscope or handheld Doppler can be performed. The American College of Obstetricians and Gynecologists (ACOG) recommends that, in intermittent auscultation of low-risk pregnancies, the fetal heart should be monitored after a contraction at least every 30 minutes during the first stage of labor and every 15 minutes in the second stage. In at-risk pregnancies, the monitoring frequency is increased to at least every 15 minutes during the first stage and to every 5 minutes in the second stage.

Important considerations in interpreting fetal heart rate data are the **baseline heart rate, variability,** and **periodic heart rate changes.** The baseline heart rate is the approximate average heart rate during a 10-minute tracing. A baseline heart rate of 110 to 160 beats/min is considered normal, less than 110 beats/min is considered to be bradycardia, and greater than 160 beats/min is considered to be tachycardia. Fetal bradycardia may occur with maternal hypothermia, certain medications given to the mother, or congenital heart block, or may be a sign of significant fetal distress. Bradycardia may also be a normal variant. The most common cause of fetal tachycardia is maternal fever. Other common causes include medications and fetal arrhythmias.

Variability is regulated by the balance of sympathetic and parasympathetic control of the sinoatrial node. **Short-term (or beat-to-beat) variability** is the change in fetal heart rate from one beat to the next and can only be accurately determined when an internal scalp electrode is placed. Normal short-term variability is 6 to 25 beats/min. **Long-term variability** is the waviness of the baseline heart rate over 1 minute, with normal oscillations occurring at a rate of 3 to 5 cycles per minute. As variability is largely a manifestation of the autonomic nervous system, anything that affects nervous system functioning can affect it. Common causes of decreased variability are fetal sleep cycles, CNS (central nervous system) depressant drugs (such as narcotic analgesics) given to the mother, congenital neurologic abnormalities, and prematurity. Fetal acidemia secondary to hypoxemia can impair CNS function and reduce variability. The presence of normal variability makes fetal acidemia unlikely.

Periodic heart rate changes are the **accelerations** and **decelerations** from the baseline heart rate that occur, often related to uterine contractions. An acceleration is an increase in the fetal heart rate of 15 beats/min or more for 15 seconds or longer and is a reassuring finding. The presence of accelerations, whether occurring spontaneously or in response to contractions, fetal movement, or stimulation of the fetus (either scalp stimulation during a cervical examination or vibroacoustic stimulation using an artificial larynx) virtually ensures that the fetal arterial pH is greater than 7.2. Decelerations are generally defined as **early, late,** or **variable** based on the timing of the deceleration in relation to a contraction. An **early deceleration** coincides with a contraction in onset of the fetal heart rate decline and return to the baseline. Early decelerations are thought to be a result of increased vagal tone caused by compression of the fetal head and are not associated with fetal hypoxia or acidemia. A **late deceleration** is a gradual reduction in the fetal heart rate that starts at or after the peak of a contraction and has a gradual return to the baseline. Late decelerations are a manifestation of uteroplacental insufficiency and can be caused by numerous circumstances. Common among these are maternal hypotension, as is often seen with epidural anesthesia and uterine hyperstimulation caused by oxytocin administration. Conditions that impair placental circulation, including maternal hypertension, diabetes, prolonged pregnancy, and placental abruption, often contribute to late decelerations. A **variable deceleration** is an abrupt decrease in fetal heart rate, usually followed by an abrupt return to baseline that occurs variably in its timing, relative to a contraction. Variable decelerations are the most common types of decelerations seen during fetal heart monitoring and are considered to be due to umbilical cord compression during contractions. Variable decelerations, particularly when there is also the presence of normal variability and accelerations, are usually not associated with fetal hypoxemia.

Current fetal monitoring equipment also allows for contraction monitoring along with the fetal heart rate assessment. An external tocodynamometer is most commonly used. It allows for evaluation of the presence and timing of contractions but does not measure the strength of the contractions. To assess the strength of contractions, an internal intrauterine pressure catheter (IUPC) can be placed. Like the fetal scalp electrode, this requires the presence of ruptured membranes. An IUPC can be useful when the first stage of labor is not progressing at an expected rate, as the frequency and power of contractions can be directly measured. Contractions that are inadequate in frequency or power may be augmented with an oxytocic agent. Intravenous oxytocin is the drug of choice, as it is effective, inexpensive, and most practitioners are familiar with its usage. Oxytocin has a short half-life, which allows it to be given by continuous infusion and allows for the rapid cessation of its activity when it is discontinued. Labor augmentation with oxytocin can cause uterine hyperstimulation, defined as the presence of 6 or more contractions in a 10-minute period that causes nonreassuring fetal heart rate abnormalities (such as late

decelerations). This would be managed by reduction in dose or discontinuation of the oxytocin, repositioning of the patient, and providing oxygen via face mask to the mother.

During labor, the fetal head descends through the birth canal and undergoes four **cardinal movements.** During initial descent, the head undergoes **flexion,** bringing the fetal chin to the chest. As descent progresses **internal rotation** occurs, causing the fetal occiput to move anteriorly toward the maternal symphysis pubis. As the head approaches the vulva it undergoes **extension,** to allow the head to pass below the symphysis pubis and through the upward-directed vaginal outlet. Further extension leads to the delivery of the head, which then restitutes via **external rotation** to face either to the maternal right or left side. This corresponds with rotation of the fetal body, aligning one shoulder anteriorly below the symphysis pubis and the other posterior toward the sacrum. Maternal pushing, along with gentle downward traction on the fetal head, will deliver the anterior shoulder, and upward traction similarly delivers the posterior shoulder. Delivery of the remainder of the body will quickly follow. Occasionally, the anterior shoulder will not readily pass below the pubic symphysis. This is called a **shoulder dystocia** and is an obstetrical emergency, requiring a coordinated effort by the entire medical team to reduce the dystocia. Maneuvers, including hyperflexion of the hips (McRoberts maneuver), suprapubic pressure, cutting an episiotomy, or rotation of the fetal body in the vaginal canal, are attempted and are usually successful.

Of deliveries in the United States, 20% or more are accomplished via cesarean delivery. The most common indications are a history of prior cesarean delivery, arrest of labor or descent, fetal distress necessitating immediate delivery, and breech presentation. Operative vaginal delivery can be performed using either forceps or vacuum assistance. These can only be used when the cervix is completely dilated, membranes are ruptured, the presenting part is the vertex of the scalp, and there is no disproportion between the size of the fetal head and maternal pelvis. If any of these conditions are not met and delivery must be accomplished urgently, a cesarean delivery is indicated.

Comprehension Questions

16.1 A 21-year-old G1 woman is admitted to the labor unit with spontaneous rupture of membranes. On initial examination, her cervix is 5 cm dilated. Four hours later, her cervix remains unchanged. Which of the following is the most likely diagnosis?

A. Prolonged latent phase
B. Arrest of active phase
C. Arrest of descent
D. Prolonged third stage of labor

16.2 Which of the following is thought to be a result of compression of the fetal head?
A. Early decelerations
B. Variable decelerations
C. Late decelerations
D. Sinusoidal heart rate pattern

16.3 A pregnant woman with an estimated gestational age of 34 weeks presents to the labor triage unit with a clear vaginal discharge. On sterile speculum examination you see a pool of watery fluid in the vagina. Microscopic examination reveals "ferning." Which of the following is the most likely diagnosis?
A. Urinary incontinency
B. Rupture of membranes
C. Bacterial vaginosis
D. *Candida* vaginitis

ANSWERS

16.1 **B.** The cervical dilation beyond 4 cm means active phase. No cervical change for 2 hours is defined as arrest of active phase.

16.2 **A.** Early decelerations are thought to be caused by fetal head compression. Variable decelerations are caused by cord compression and late decelerations by uteroplacental insufficiency.

16.3 **B.** A pool of clear fluid with ferning noted on an air-dried microscopic slide is diagnostic of rupture of fetal membranes. In this case, as she is 34-week gestation, it represents preterm rupture of membranes.

Clinical Pearls

- The presence of accelerations on a fetal heart tracing is very reassuring and consistent with a fetal pH of 7.2 or more.
- The use of universal, prenatal screening for group B *Streptococcus* and provision of intrapartum antibiotics to women who are colonized can reduce the risk of GBS disease in infants by approximately 50%.
- Fetal heart rate tracings must be interpreted within the overall clinical situation. Reduction in variability shortly after giving a narcotic pain medication may represent fetal sleep cycle; reduction in variability along with repetitive late decelerations may be an ominous sign of fetal distress.

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Case 17

A 58-year-old woman presents to your office for follow-up of an emergency department visit. She was seen 1 week earlier in the emergency department for abdominal pain and was diagnosed with nephrolithiasis. Ultimately, she was sent home with pain medications and given instructions to strain her urine for stones and to follow up with her primary care physician. Today, she is asymptomatic. She takes no medications on a regular basis. Her family history is significant only for a father with high blood pressure. She had several routine labs drawn in the emergency department, copies of which she brings with her. Upon your review of the labs, you note the following (normal values are in parenthesis): sodium 142 mEq/L (135-145); potassium 4.0 mEq/L (3.5-5.0); chloride 104 mg/dL (95-105); bicarbonate 28 mEq/L (20-29); blood urea nitrogen (BUN) 20 mg/dL (7-20); creatinine 0.9 mg/dL (0.8-1.4); calcium 12.5 mg/dL (8.5-10.2); albumin 4.2 g/dL (3.4-5.4). The complete blood count (CBC) was within normal limits.

The renal calculus was detected by helical CT scanning without contrast and was midureter on the right.

Your patient has brought with her the stone that she has strained from the urine. Upon questioning, you learn that she has had multiple episodes of "kidney stones" in the past 2 years. You send the stone to the lab for analysis and order a repeat serum calcium level. The results show that the stone is made of calcium oxalate the serum calcium is still elevated at 11.9 mg/dL.

- What is your diagnosis?
- What is the most likely cause?
- What is the next step?

ANSWERS TO CASE 17:
Calcium Disorders

Summary: This is a 58-year-old woman with a history of recurrent nephrolithiasis, presenting for follow-up and found to have calcium oxalate stones. She had an initial serum calcium level that was elevated, as was the repeat serum calcium 1 week later. At the time of her follow up, she was completely asymptomatic. She takes no medications, and has a family history only significant for hypertension.

- **Diagnosis:** Hypercalcemia and recurrent nephrolithiasis
- **Most likely cause:** Hyperparathyroidism
- **Next step:** Further laboratory workup, including serum parathyroid hormone (PTH)

ANALYSIS

Objectives

1. Be familiar with the differential diagnosis of hypercalcemia, especially the most common etiologies.
2. Understand the workup of hypercalcemia.
3. Learn the basics of calcium regulation.
4. Learn about management options of hyperparathyroidism.

Considerations

This patient illustrates one common presentation of hypercalcemia. Many times, patients with hypercalcemia are asymptomatic and an elevated calcium level is found unexpectedly on routine labs. The diagnostic workup begins with a careful review of the patient's history, as clues to its etiology may often be elicited here. The diagnostic workup is designed to distinguish parathyroid dysfunction from other etiologies so that optimal treatment and management can be pursued.

APPROACH TO
Calcium Disorders

DEFINITIONS

HYPERPARATHYROIDISM: Condition of elevated parathyroid hormone usually due to excessive production by the parathyroid glands, leading to hypercalcemia.

SECONDARY HYPERPARATHYROIDISM: Condition as the parathyroid glands overproduce PTH to respond to low serum calcium levels. This may occur as a response to low dietary calcium intake or a deficiency of vitamin D.

TERTIARY HYPERPARATHYROIDISM: Elevated PTH in patients who have renal failure.

CLINICAL APPROACH

Pathophysiology of Calcium Homeostasis

Before discussing the differential diagnosis of hypercalcemia, it is essential to review the basic mechanism by which normal calcium levels are maintained in the body. **Most of the calcium in the body is found in the skeleton** (approximately 98%). The remaining calcium is found in circulation. Of this remaining 2%, about half is bound to albumin and other proteins, and half is "free," or ionized. It is the ionized calcium that has physiologic effects. Because the serum calcium is partially bound to albumin, abnormally low serum albumin levels will affect the measurement of calcium, thus causing a misinterpretation of an abnormal calcium level. With patients found to have a concomitant hypoalbuminemia, the ionized calcium can be measured directly. However, there is a useful formula that can correct for this error. A "corrected" serum calcium is provided by the formula:

$$\text{"Corrected" serum calcium} = [(\text{Normal albumin}) \times (\text{Patient's albumin level})] \times [0.8 \times (\text{serum calcium})]$$

PTH, calcitonin, and 1,25-dihydroxyvitamin D_3 (calcitriol) are responsible for regulating calcium levels and maintaining calcium homeostasis. **Causes of hypercalcemia include an increase in calcium resorption from bone, decreased renal excretion of calcium, or an increase in calcium absorption from the gastrointestinal tract.** When calcium levels increase, calcitonin, produced by the thyroid parafollicular cells, attempts to lower calcium levels through renal excretion of calcium and by opposing osteoclast activation. When calcium is excreted through this pathway, phosphate is also excreted. Conversely, low levels of circulating calcium normally result in PTH secretion. This promotes

osteoclast activation, which mobilizes calcium from bone and effects calcium resorption at the kidneys, thereby retaining circulating calcium. While PTH will increase the calcium in the blood, it has the opposite effect on serum phosphate levels. PTH also increases calcitriol levels, which act at the gastrointestinal tract to promote both calcium and phosphate absorption.

HYPERCALCEMIA

Etiology

Any process that increases gastrointestinal calcium absorption, decreases renal excretion, or activates osteoclastic activity will raise serum calcium levels. If this occurs beyond the normal bounds of maintaining calcium homeostasis, hypercalcemia will occur. **The most common cause of hypercalcemia in the ambulatory patient is hyperparathyroidism.** Cancer ranks as the second leading cause, as hypercalcemia is often an early manifestation of malignancy. Hyperparathyroidism and cancer combined account for 90% of hypercalcemia cases. It is useful to categorize the etiologies of hypercalcemia into five main areas: parathyroid hormone-related, malignancy, renal failure, high bone turnover, and those related to Vitamin D (Table 17–1).

Clinical Manifestations of Hypercalcemia

Normal values of serum calcium range from 8 to 10 mg/dL, which correspond to an ionized calcium level of 4 to 5.6 mg/dL. Levels of serum calcium between 10.5 and 12 mg/dL are classified as mild hypercalcemia; patients are frequently asymptomatic at these levels. As calcium levels increase, physical manifestations may become apparent. The classic mnemonic, "stones, bones, psychic groans, and abdominal moans" is useful to categorize the constellation of physical symptoms associated with hypercalcemia (Table 17–2). Other clinical manifestations include the cardiac sequelae of shortening QT interval and arrhythmias.

Diagnostic Approach

The diagnostic approach to hypercalcemia begins with a careful history, including the manifestations of elevated calcium levels. When the aforementioned etiologies are taken into consideration, it becomes clear that the history should include family history of calcium disorders, such as renal stones or malignancy. The patient's risk factors for malignancy, such as smoking, should be investigated. A careful review of medications should also take place, to include not only prescription medications but also over-the-counter supplements. Dietary history is also an important component. At this point, if the hypercalcemia is mild and the patient asymptomatic, it is acceptable to stop the suspect medication and repeat the serum calcium level.

Table 17–1 COMMON CAUSES OF HYPERCALCEMIA

CONDITION	SPECIFIC EXAMPLE	PATHOPHYSIOLOGY
Increased Bone Resorption		
Primary hyperparathyroidism	Sporadic or familial; multiple endocrine neoplasia (types I and II)	
Malignancy	Solid tumors of lung; squamous carcinoma of head and neck; renal carcinoma	Tumor secretion of **PTH-rP**
	Breast cancer; multiple myeloma; prostate cancer	Direct osteolysis
Hypervitaminosis A (vitamin A intoxication)	Includes both vitamin A and its analogs (used to treat acne)	Increased bone resorption
Immobilization	Less common than above causes	Increased risk when underlying disorder of high bone turnover (eg, Paget disease)
Increased Calcium Absorption		
Hypervitaminosis D (vitamin D intoxication)		Increased calcitriol level leads to increased GI absorption of calcium and phosphate
Granulomatous disease	Tuberculosis; sarcoidosis; Hodgkin disease	Increase extrarenal conversion of 25-hydroxyvitamin D_3 to calcitriol
Milk alkali syndrome		Excessive intake of calcium-containing antacids
Miscellaneous		
Medications	Thiazide diuretics Lithium	Reduced urinary excretion of calcium; increased PTH secretion
Rhabdomyolysis		Calcium released from injured muscle
Adrenal insufficiency		Increased bone resorption and increased protein binding of calcium
Thyrotoxicosis (usually mild hypercalcemia)		Increased bone resorption

Abbreviation: PTH-rP, parathyroid hormone-related peptide.

Table 17–2 PHYSICAL MANIFESTATIONS OF HYPERCALCEMIA

	SYMPTOM/SIGNS
Stones	Renal calculi
Bones	Bone pain, including arthritis and osteoporosis
Psychic groans	Poor concentration, weakness, fatigue, stupor, coma
Abdominal moans	Abdominal pain, constipation, nausea, vomiting, pancreatitis, anorexia

The next step, if a causative medication is not found, is to measure a serum intact PTH level. This level will either be suppressed, normal, or elevated. As with many endocrine disorders, **it is useful not to think of normal or abnormal values; rather, one should understand what is appropriate for a given situation.** For example, in normal subjects, an increased calcium load will normally depress the PTH hormone level, thus a low PTH level in this situation is *normal,* or appropriately suppressed. If a patient has an elevated calcium level and the PTH is "normal," it is said to be inappropriately normal, because in the face of hypercalcemia it should be low, or suppressed.

If our patient with hypercalcemia has a normal or elevated PTH level, then the normal feedback loop is not responding. In this situation, the pituitary is producing PTH without check, which, in turn, is elevating the calcium level. This is hyperparathyroidism. Primary hyperparathyroidism occurs when the parathyroid gland overproduces PTH and does not respond to the negative feedback of elevated calcium levels. **The vast majority of primary hyperparathyroidism is caused by an adenoma (benign tumor) of one of the four parathyroid glands.**

Secondary hyperparathyroidism occurs as the parathyroid glands overproduce PTH to respond to low serum calcium levels. This may occur as a response to low dietary calcium intake or a deficiency of vitamin D. Tertiary hyperparathyroidism occurs in patients who have renal failure. Patients in renal failure usually present with *hypo*calcemia, hyperphosphatemia, and low vitamin D levels. If this is untreated, it leads to hyperplasia of the parathyroid glands, an increased PTH secretion, and subsequent hypercalcemia.

There is a condition that can produce inappropriately high PTH levels unrelated to the parathyroid production. This is familial hypocalciuric hypercalcemia (FHH), a genetic disorder related to a defect in a gene that codes for a calcium-sensing receptor. Consequently, simply measuring PTH alone may confound this diagnosis, which may be mistaken for primary hyperparathyroidism. To distinguish these entities, a 24-hour urinary calcium level is obtained.

In hyperparathyroidism, the kidneys spill calcium into the urine at a normal or elevated level. With FHH the urinary calcium level is low.

A PTH level that is low with elevated serum calcium suggests that the parathyroid gland is responding appropriately to the high calcium environment. The etiology in this scenario must be some process that causes calcium to be released from bone or calcium to be absorbed from the gut despite the suppressed PTH. This is seen when tumors produce a hormone that mimics the active site of the PTH molecule, particularly in respect to the bone and renal effects, but that have no counter regulatory mechanism for suppression when calcium levels rise. This molecule is called parathyroid hormone-related peptide (PTH-rP). PTH-rP is produced by lung cancers, squamous cell cancers of the head and neck, and renal cell cancer. PTH-rP effects osteoclastic bone resorption, increases calcitriol, and promotes calcium resorption from the kidneys, resulting in increased levels of serum calcium. The continued production of PTH-rP effectively takes the parathyroid gland out of the loop in calcium homeostasis. Because cancer is a common etiology for hypercalcemia, the **search for malignancy is paramount at this step in diagnosis, before other, less common, disorders are considered.**

If a malignancy is not found, other etiologies must be considered. These fall into the category of endocrine disorders other than parathyroid and include hyperthyroidism, adrenal insufficiency, and acromegaly. The workup thus includes thyroid-stimulating hormone (TSH), a cortisol level, and a pituitary imaging study, respectively.

Treatment of Hypercalcemia

The **treatment of hypercalcemia is directed at the underlying disorder.** Patients with mild hypercalcemia may be treated with preventative measures aimed at avoiding aggravating factors. These measures include adequate hydration (dehydration aggravates nephrolithiasis), avoiding thiazide diuretics or other offending medications, encouraging physical activity, and avoiding prolonged inactivity. Other interventions for mild hypercalcemia are disease specific.

For the treatment of primary hyperparathyroidism, surgical parathyroidectomy is the definitive treatment. Surgery is appropriate for patients with symptomatic hyperparathyroidism. Surgery may be an option for selected asymptomatic patients, including those who have developed osteoporosis or renal insufficiency, who have markedly elevated calcium levels, or who are younger than age 50 years.

Comprehension Questions

17.1 A 60-year-old man comes into your office with the complaint of fatigue and constipation. He has had no dietary changes recently. A history reveals that he has hypertension, treated with medications, and an inguinal hernia that was repaired 10 years earlier without complications. The examination was nonspecific. You decide to obtain an electrolyte panel and find that the calcium level is elevated at 11.5 mg/dL (normal 8.5-10.2). Other labs were normal. Which of the following is the next step?

A. Consult vascular surgery for placement of a dialysis catheter and schedule for dialysis.
B. Advise the patient to drink plenty of fluids and repeat the labs in 1 month.
C. Explore the patient's hypertension, including what medications he takes.
D. Obtain a chest x-ray, looking for possible malignancy.

17.2 A 48-year-old man presents for follow-up of an elevated calcium level of 12.3 mg/dL found on routine screening labs at his last well-man visit. He takes no medications other than an occasional antihistamine for allergies. He recently started smoking a half-pack of cigarettes per day. He was prompted to attend to his well-man visit by his wife who claims that he has become forgetful, has a decreased appetite, and has had a 10-lb weight loss over the past 2 months. As part of his follow-up labs, you obtain a serum PTH, which comes back within the normal range. Which of the following is the next step in diagnosis?

A. Chest x-ray
B. Repeat calcium after hydration
C. Measurement of PTH-rP levels
D. Measurement of urinary calcium excretion

17.3 You obtain follow-up labs for a hypercalcemic patient and find that the PTH level is suppressed. There are no suspect medications. You suspect lung cancer based on a 30 pack-year smoking history, but the chest x-ray is normal. Which of the following is the next most appropriate step?

A. Continue a malignancy workup.
B. Check TSH, as a thyroid disorder may be the cause.
C. Refer the patient to an endocrinologist, as hypercalciuric hypercalcemia is an exceedingly rare genetic cause of an elevated calcium that requires specialist care.
D. Measure urinary calcium excretion.

ANSWERS

17.1 **C.** When presented with a patient who has elevated calcium levels, the first step is to determine if there are any causative medications. Hydrochlorothiazide is a commonly used antihypertensive medication that may contribute to elevated calcium levels (thiazide diuretic).

17.2 **D.** This patient has symptomatic hypercalcemia. He has an inappropriately normal PTH level, which should be suppressed with this degree of hypercalcemia. The next step is to measure a 24-hour urinary calcium excretion to determine if this condition represents primary hyperparathyroidism (most common) or familial hypocalciuric hypercalcemia (rare).

17.3 **A.** In a hypercalcemic patient, a suppressed PTH first should be considered a sign of malignancy until proven otherwise. A chest x-ray is insufficient to rule out malignancy, as there are other malignancies that can cause hypercalcemia, mediated either by way of PTH-rP or through direct osteoclastic bone resorption. Multiple myeloma, granulomatous disease such as tuberculosis, sarcoidosis, and Hodgkin lymphoma, breast cancer, and squamous cell cancers of the head and neck can cause an elevated calcium with an appropriately suppressed PTH.

Clinical Pearls

- Be sure to question any patient with hypercalcemia regarding all medications—both prescription and over-the-counter—as both megadose vitamins (A and D) and excessive use of calcium carbonate antacids may play a role.
- Most cases of primary hyperparathyroidism occur in postmenopausal women, who are often already at increased risk of osteoporosis. Be sure to check their bone density with a dual-energy x-ray absorptiometry (DEXA) scan.
- Hypercalcemia with a suppressed PTH should be considered malignancy until you can prove otherwise.

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Case 18

A 75-year-old white man presents for a health maintenance check-up. The patient has stable hypertension but has not seen a physician in more than 2 years. He denies any particular problems. He lives alone. He takes an aspirin a day and is compliant with his blood pressure medication (hydrochlorothiazide). His son fears that his father is either experiencing a stroke or getting Alzheimer disease because his father is having trouble with speech discrimination and understanding what family members are saying during social events. The son reported no noticeable weakness or gait impairment. On physical examination, the patient's blood pressure was 130/80 mm Hg. Examination of the ears showed no cerumen impaction and normal tympanic membranes. His general examination is normal. Laboratory studies, including thyroid-stimulating hormone (TSH), are normal.

- What is the most likely diagnosis?
- What is the next step?

ANSWERS TO CASE 18:
Geriatric Health Maintenance

Summary: A 75-year-old man who presents with loss of speech discrimination and complains of difficulty understanding speech and conversation in noisy areas

- **Most likely diagnosis:** Presbycusis.
- **Next step:** Presbycusis is a diagnosis of exclusion. Hearing aids are underused in presbycusis but are potentially beneficial for most types of hearing loss, including sensorineural hearing loss. Consequently, referral to an audiologist for testing and consideration of amplification with a hearing aid may be an important next step.

ANALYSIS

Objectives

1. Be familiar with geriatric health maintenance.
2. Be aware of the importance of geriatric screening.

Considerations

The patient described in the case is a 75-year-old man who has difficulty with speech discrimination and complains of difficulty understanding speech and conversation in noisy areas. He most likely has presbycusis, which is an age-related sensorineural hearing loss typically associated with both selective high-frequency loss and difficulty with speech discrimination. Physical examination of the ears in patients with presbycusis is normal. Other conditions in the differential diagnosis include cerumen impaction, otosclerosis, and central auditory processing disorder. Cerumen impaction and otosclerosis can be diagnosed by otoscopy. Central auditory processing disorder is diagnosed when the patient can hear sounds without difficulty, but has difficulty in understanding spoken words.

APPROACH TO
Health Maintenance in the Elderly

DEFINITIONS

PRESBYCUSIS: An age-related sensorineural hearing loss typically associated with both selective high-frequency loss and difficulty with speech discrimination.

FUNCTIONAL ASSESSMENT: An evaluation process that gauges a patient's ability to manage tasks of self-care, household management, and mobility.

CLINICAL APPROACH

By the year 2030 the number of people aged 65 years and older is expected to double from what it was in 1999, increasing from 34 million to 69 million. Geriatric health maintenance provides screening and therapy with the goal of enhancing function and preserving health in the elderly. Screening is not indicated unless early therapy for the screened condition is more effective than late therapy or no therapy. **Preventive services for the elderly include as goals the optimization of quality of life, satisfaction with life, and maintenance of independence and productivity.** Most recommendations for patients older than age 65 years overlap recommendations for the general adult population. Certain categories are unique to older patients, including sensory perception and accident. The primary care physician can perform effective health screening using simple and relatively easily administered assessment tools **(Figure 18–1)**

Functional Assessment

Functional assessment gauges a patient's ability to manage tasks of self-care, household management, and mobility. Impairment in activities of daily living results in an increased risk of falls, hip fracture, depression, and institutionalization. An estimated **25% of patients older than age 65 years have impairments in their instrumental activities of daily living (IADL) or activities of daily living (ADL) (Table 18–1)** Persons who are unable to perform IADL independently are far more likely to have dementia than their independent counterparts.

Vision Screening

Visual impairment is an independent risk factor for falls, which has a significant impact on quality of life. Direct visual testing with a Snellen chart or Jaeger card is the most sensitive and specific approach to visual screening. Referring all older people for a complete eye examination has the advantages of improving the quality of the examination and allowing for cataract and glaucoma screening. The majority of conditions leading to vision loss in the elderly are presbyopia, macular degeneration, glaucoma, cataract, and diabetic retinopathy.

The incidence of presbyopia increases with age. Patients have difficulty focusing on near objects while their distant vision remains intact. **Age-related macular degeneration (AMD) is the leading cause of severe vision loss in the elders.** AMD is characterized by atrophy of cells in the central macular region

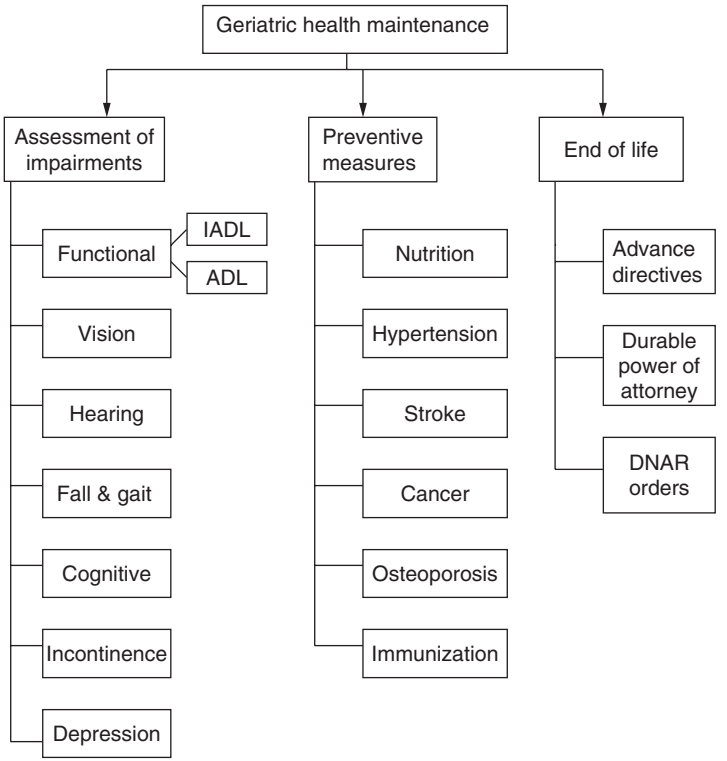

Figure 18–1. Approach to geriatric health maintenance. ADL, activities of daily living; DNAR, do not attempt resuscitation; IADL, instrumental activities of daily living.

Table 18–1 INSTRUMENTAL ACTIVITIES OF DAILY LIVING (IADL) AND ACTIVITIES OF DAILY LIVING (ADL)

IADL	ADL
Transportation	Bathing
Shopping	Dressing
Cooking	Eating
Using the telephone	Transferring from bed to chair
Managing money	Continence
Taking medications	Toileting
Housecleaning	
Laundry	

of the retinal pigment epithelium, resulting in the loss of central vision. Glaucoma is characterized by a group of optic neuropathies that can occur in all ages. Although glaucoma is most often associated with elevated intraocular pressure, it is the optic neuropathy that defines the disease. Cataract is any opacification of the lens. Age-related, or senile, cataracts account for 90% of all cataracts. **Cataract disease is the most common cause of blindness worldwide.** Diabetic retinopathy is the leading cause of blindness in working-age adults in the United States. It is important to consider diabetic retinopathy in geriatric vision screening.

Hearing Screening

More than one-third of persons older than age 65 years and half of those older than age 85 years have some hearing loss. This deficit is correlated with social isolation and depression. The whispered voice test has sensitivities and specificities ranging from 70% to 100%. The initial office screening for general hearing loss can be reliably performed with questionnaire such as the HHIE-S (Hearing Handicap Inventory for the Elderly). Limited office-based pure-tone audiometry is more accurate in identifying patients who would benefit from a more formal audiometry.

The majority of patients with hearing impairment will present with complaints unrelated to their sensory deficit. In a quiet examination room with face-to-face conversation, patients can overcome significant hearing loss and avoid detection from a physician. Family members are often more concerned about the hearing loss than the patient. **Common causes of geriatric hearing impairments are presbycusis, noise-induced hearing loss, cerumen impaction, otosclerosis, and central auditory processing disorder.** Presbycusis is age-related sensorineural hearing loss usually associated with both selective high-frequency loss and difficulty with speech discrimination. Presbycusis is the most common form of hearing loss in the elderly. Because it often goes unrecognized, exact prevalence data are lacking. Presbycusis is a diagnosis of exclusion. Complete deafness is not an expected end result of presbycusis. Noise-induced hearing loss is essentially a wear and tear phenomenon that can occur with either industrial or recreational noise exposure. Patients will typically present with tinnitus, difficulty with speech discrimination, and problems hearing background noise. Cerumen impaction in the external auditory canal is a common, frequently overlooked problem in the elderly that may produce a transient, mild conductive hearing loss. It is estimated that 25% to 35% of institutionalized or hospitalized elderly are affected by impacted cerumen. Otosclerosis is an autosomal dominant disorder of the bones in the inner ear. It results in progressive conductive hearing loss with onset most commonly in the late twenties to the early forties. Speech discrimination is typically preserved. Geriatric patients with hearing loss may have otosclerosis complicating their presentation. Central auditory processing disorder (CAPD) is the general term for conditions involving

hearing impairment that results from CNS dysfunction. The patient with CAPD will have difficulty understanding spoken language, but may be able to hear sounds well.

Fall Assessment

Falls are the leading cause of nonfatal injuries in the elderly. The associated complications are the leading cause of death from injury in those older than age 65 years. Hip fractures are common precursors to functional impairment and nursing home placement. Approximately **30% of the noninstitutionalized elderly fall each year.** The annual incidence of falls approaches 50% in patients older than 80 years of age. Factors contributing to falls include age-related postural changes, alterations in visual ability, certain medications, and diseases affecting muscle strength and coordination. Every older person should be asked about falls, as many will not volunteer such information. Gait impairments commonly coexist with falls.

Cognitive Screening

The prevalence of dementia doubles every 5 years after age 60, so that by age 85 approximately 30% to 50% of individuals have some degree of impairment. Patients with mild or early dementia frequently remain undiagnosed because their social graces are retained. **The combination of the "clock draw" and the "three-item recall" is a rapid and fairly reliable office-based screening for dementia**. When patients fail either of these screening tests, further testing with the Folstein Mini-Mental State questionnaire should be performed.

Incontinence Screening

Incontinence in the elderly is common. Incontinence is estimated to affect 11% to 34% of elderly men and 17% to 55% of elderly women. Continence problems are frequently treatable, have major social and emotional consequences, but are often not raised by patients as a concern.

Depression Screening

Depressive symptoms are more common in the elderly despite major depressive disorder being slightly lower in prevalence when compared with younger populations. **Unlike dementia, depression is usually treatable.** Depression significantly increases morbidity and mortality, and is often overlooked by physicians. A simple two-question screen (*Have you felt down/depressed/hopeless in the last 2 weeks?* and *Have you felt little interest or pleasure in doing things?*) shows high sensitivity. Positive responses can be followed up with a Geriatric Depression Scale, a 30-question instrument that is sensitive, specific, and reliable for the diagnosis of depression in the elderly.

Nutrition Screening

Approximately 15% of older outpatients and half of the hospitalized elderly are malnourished. **A combination of serial weight measurements obtained in the office and inquiry about changing appetite are likely the most useful methods of assessing nutritional status in the elderly.** Adequate calcium intake for women is advised. Supplementation with a multivitamin formulated at about 100% daily value can decrease the prevalence of suboptimal vitamin status in older adults and improve their micronutrient status to levels associated with reduced risk for several chronic diseases. Malnutrition is common in nursing homes, and protein undernutrition has a prevalence of 17% to 56% in this setting. Protein undernutrition is associated with an increased risk of infections, anemia, orthostatic hypotension, and decubitus ulcers.

Hypertension Screening

Treatment of hypertension is of substantial benefit in the elderly. Heart disease and cerebrovascular disease are leading causes of death in the elderly. Treatment of hypertension has contributed to a reduction in mortality from both stroke and coronary artery disease. Lifestyle modifications are recommended for all hypertensive patients. Thiazides are the drugs of choice unless a comorbid condition makes another choice preferable.

Stroke Prevention

The incidence of stroke in older adults roughly doubles with each 10 years of age. The greatest risk factor is hypertension followed by atrial fibrillation. Anticoagulation with warfarin reduces the risk of strokes in people with atrial fibrillation, but many elderly patients are not anticoagulated because of the fear of injuries from falls. In most instances, the benefits of anticoagulation are likely to outweigh the increased risk of fall-related bleeding, unless the patient has multiple falls, high-risk falls, or a very low risk of stroke.

Cancer Screening

Screening elderly men for prostate cancer is not routinely recommended, as it has not been definitively shown to prolong life and because of the risk of incontinence or erectile dysfunction caused by the treatments. An older woman should undergo annual mammography until her life expectancy falls below 5 to 10 years. Screening for colon cancer (either with colonoscopy every 10 years or with annual fecal occult testing plus flexible sigmoidoscopy every 5 years) can be stopped when a patient's life expectancy is less than 5 to 10 years.

Osteoporosis Screening

The prevalence of low bone mineral density in the elderly is high, with osteopenia found in 37% of postmenopausal women. Primary prevention of osteoporosis begins with identification of risk factors (older age, female gender, white or Asian race, low calcium intake, smoking, excessive alcohol use, and chronic glucocorticoid use). Calcium carbonate (500 mg three times daily) and vitamin D (400-800 IU/d) reduce the risk of osteoporotic fractures in both men and women. Bone mineral density testing using dual-energy x-ray absorptiometry (DEXA) of patients with multiple risk factors may uncover asymptomatic osteoporosis.

Immunizations

Individuals older than age 65 years should receive annual influenza vaccination. Similarly, persons older than age 65 should receive at least one pneumococcal immunization and a single booster dose of tetanus and diphtheria vaccine. One dose of herpes zoster vaccine is recommended at age 60 or older.

END OF LIFE ISSUES

Advance Directives

Well-informed, competent adults have a right to refuse medical intervention, even if refusal is likely to result in death. To further patient autonomy, physicians are obligated to inform patients about the risks, benefits, alternatives, and expected outcomes of end-of-life medical interventions such as cardiopulmonary resuscitation, intubation and mechanical ventilation, vasopressor medication, hospitalization and ICU care, and artificial nutrition and hydration. **Advance directives are oral or written statements made by patients when they are competent that are intended to guide care should they become incompetent.** Advance directives allow patients to project their autonomy. Although oral statements about these matters are ethically binding, they are not legally binding in all states. Written advance directives are essential so as to give effect to the patient's wishes in these matters.

Durable Power of Attorney for Health Care (DPOA-HC)

A durable power of attorney allows the patient to designate a surrogate decision maker. The responsibility of the surrogate is to provide "substituted judgment" to decide as the patient would, not as the surrogate wants. In the absence of a designated surrogate, physicians turn to family members or next of kin, under the assumption that they know the patient's wishes.

Do Not Attempt Resuscitation (DNAR) Orders

Physicians should encourage patients to express their preferences for the use of cardiopulmonary resuscitation (CPR). Despite the favorable portrayal of CPR in the media, **only approximately 15% of all patients who undergo CPR in the hospital survive to hospital discharge.** DNAR ("do not attempt resuscitation") is the preferred term over DNR ("do not resuscitate) to emphasize the low likelihood of successful resuscitation. In addition to mortality statistics, patients deciding about CPR preferences should also be informed about the possible consequences of surviving a CPR attempt. CPR may result in fractured ribs, lacerated internal organs, and neurologic disability. There is also a high likelihood of requiring other aggressive interventions if CPR is successful. For some patients at the end of life, decisions about CPR may not be about whether they will live but about how they will die.

Comprehension Questions

18.1 A third-year medical student is researching various recommendations for the care of the geriatric patient. Which of the following statements is most accurate?

A. The American Urological Association (AUA) and United States Preventive Services Task Force (USPSTF) recommend annual prostate cancer screening with digital rectal examination (DRE) and prostate-specific antigen (PSA).
B. All men older than age 50 years should have a PSA drawn each year, regardless of other health conditions.
C. The United States Preventive Services Task Force (USPSTF) concludes that the evidence is insufficient to recommend for or against routine screening for prostate cancer with digital rectal examination (DRE) and prostate-specific antigen (PSA).
D. Transrectal ultrasound offers the greatest sensitivity and specificity for detecting prostate cancer.
E. For healthy men older than age 70 years, the AUA discourages any prostate cancer screening.

18.2 A 70-year-old man is having difficulty hearing his family members' conversations. He is diagnosed with presbycusis. Which of the following statements regarding his condition is most accurate?

A. Presbycusis does not respond to hearing aid use.
B. Presbycusis is usually caused by a conductive disorder.
C. Presbycusis usually results in loss of speech discrimination.
D. Presbycusis usually results in unilateral hearing loss.
E. Presbycusis usually results in low-frequency hearing loss.

18.3 Which of the following is the leading cause of blindness worldwide?
A. Glaucoma
B. Vitamin A deficiency
C. Age-related, or senile, cataracts
D. Diabetic retinopathy

ANSWERS

18.1 **C.** The combination of DRE and PSA is known to increase the sensitivity and specificity of prostate cancer detection. However, the benefit of routine use of checking prostate-specific antigen and rectal examination to detect prostate cancer is questionable. It is a Category I recommendation.

18.2 **C.** Up to one-third of persons older than age 65 years suffer from hearing loss. Presbycusis typically presents with symmetric high-frequency hearing loss. There is loss of speech discrimination, so that patients complain of difficulty understanding rapid speech, foreign accents, and conversation in noisy areas. The mechanism is sensorineural rather than a conductive problem.

18.3 **C.** The vast majority of cataracts are age related, although there are other causes. Cataracts are the leading cause of blindness worldwide. Diabetic retinopathy is the leading cause of blindness in working-age adults in the United States. Age-related macular degeneration is the most common cause of severe vision loss in the elderly.

Clinical Pearls

- Protein undernutrition is associated with an increased risk of infections, anemia, orthostatic hypotension, and decubitus ulcers.
- Smoking is associated with osteoporosis.
- If "osteoporotic" fractures, such as vertebral compression fractures, occur in conjunction with osteopenia on x-ray, the diagnosis of osteoporosis is almost certain.
- Hearing loss, and sensory impairments in general, can be confused with cognitive impairment or an affective disorder.
- Presbyopia, macular degeneration, glaucoma, cataracts, and diabetic retinopathy account for the majority of conditions leading to vision loss in the elderly.

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Case 19

A 45-year-old man presents to the clinic with a cough productive of purulent sputum of 3-week duration. He says that he had just gotten over a cold a few weeks prior to this episode. He occasionally has fevers and he coughs so much that he has chest pain. He reports having a mild sore throat and nasal congestion. He has no history of asthma or of any chronic lung diseases. He denies nausea, vomiting, diarrhea, and any recent travel. He denies any smoking history. On examination, his temperature is 98.6°F (37.0°C), his pulse is 96 beats/min, his blood pressure is 124/82 mm Hg, his respiratory rate is 18 breaths/min, and his oxygen saturation is 99% on room air. Head, ears, eyes, nose, and throat (HEENT) examination reveals no erythema of the posterior oropharynx, tonsillar exudates, uvular deviations, or significant tonsillar swelling. Neck examination is negative. The chest examination yields occasional wheezes but normal air movement is noted.

- What is the most likely diagnosis?
- What is your next step?
- What are some common noninfectious causes of cough?

ANSWERS TO CASE 19:
Acute Bronchitis

Summary: A 45-year-old man, who has no history of lung disease and does not smoke, with 3 weeks of productive cough following an upper respiratory infection.

- **Likely diagnosis:** Acute bronchitis.
- **Next step:** Bronchodilators, analgesics, antitussives; antibiotics have not been consistently shown to be beneficial. The illness is usually self-limited.
- **Common noninfectious causes of cough:** Asthma, chronic obstructive pulmonary disease (COPD), malignancy, postnasal drip, gastroesophageal reflux disease (GERD), medication side effect (eg, angiotensin-converting enzyme inhibitors), congestive heart failure.

ANALYSIS

Objectives

1. Develop a differential diagnosis of cough persisting for 3 weeks or more.
2. Understand that most upper respiratory infections are self-limited illnesses.
3. Develop an approach for rational prescription of antibiotics for respiratory infections.

Considerations

The patient described in the case is a 45-year-old man with no prior history of lung disease, immunocompromised state, or tobacco use. These risk factors are important considerations since respiratory complains in the setting of COPD or HIV or a smoking history require a higher index of suspicion of lower respiratory tract infections such as pneumonia. As with any respiratory complaint, the ABCs should be considered; that is airway and breathing. In the ambulatory setting, a very quick assessment of the patient's distress level, respiratory use or nonuse of accessory muscles, anxiety level, stridor, and ability to speak sentences helps to triage to acute emergency versus more relaxed assessment. The individual described is afebrile, has a normal respiratory rate, and appears to be comfortable. The lung examination reveals some slight wheezes but otherwise normal breath sounds and air movement. The most likely diagnosis in this setting is acute bronchitis. Chest radiograph is not necessarily indicated; however, since the complaint has persisted for 3 weeks, any other abnormal finding such as dullness on percussion of the chest, history of fever, or clinical suspicion would be sufficient reason for chest x-ray.

Most acute bronchitis is caused by viruses and antibiotic therapy is not helpful. This patient is best treated by bronchodilator therapy such as albuterol and antitussive agents and follow-up in 2 to 3 weeks.

APPROACH TO
Upper Respiratory Infections

DEFINITIONS

ACUTE BRONCHITIS: Inflammation of the tracheobronchial tree.

PNEUMONIA: Inflammation or infection of the lower respiratory tract, involving the distal bronchioles and alveoli.

CLINICAL APPROACH

Acute Bronchitis

Acute bronchitis refers to inflammation of the tracheobronchial tree. The inflammatory response to the trigger, whether infectious, allergic, or irritant, leads to increased mucous production and airway hyperresponsiveness. As bronchitis most commonly occurs in the setting of an upper respiratory illness, it is seen more frequently in the winter. Influenza, parainfluenza, adenovirus, rhinovirus, other viruses, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae* have been implicated as causes.

As the primary symptoms are nonspecific, other etiologies can be mistakenly diagnosed as acute bronchitis. In one study, one-third of patients who had been determined to have recurrent bouts of acute bronchitis were eventually identified as having asthma. Occupational history may be important in determining whether irritants play a role.

There are no specific diagnostic criteria for acute bronchitis, although cough productive of purulent sputum is the most common presentation. Other symptoms are often present, including fever, malaise, rhinorrhea or nasal congestion, sore throat, wheezing, dyspnea, chest pain, myalgias, or arthralgias. The sputum produced can be of variable color and consistency; **the color of sputum is not diagnostic of the presence of a bacterial infection.**

The physical examination in bronchitis is typically nonspecific and, frequently, is normal. The presence of fever, tachypnea, tachycardia, and hypo- or hypertension should be noted. In persons with underlying pulmonary or cardiac conditions, or in persons with more severe symptoms, oxygen saturation by pulse oximetry may be warranted. Examination of the lungs may reveal rales, rhonchi, or wheezes, but in most cases is unremarkable.

Occasionally, findings on examination may suggest a particular etiology or an alternate diagnosis. Prolonged fever and signs of consolidation on pulmonary examination may suggest a diagnosis of pneumonia. When pneumonia is suspected, a chest radiograph should be obtained to confirm the diagnosis. Conjunctivitis and adenopathy suggest adenoviral infection, although these findings are not specific.

Bronchitis is nearly always self-limited in an otherwise healthy individual. Although most acute bronchitis lasts for less than 2 weeks, in some cases the cough can last for 2 months or more. Severe cases occasionally produce deterioration in patients with significant comorbid conditions.

Treatment

The use of antibiotics has not been shown consistently to alter the natural history of acute bronchitis, except in the uncommon case of infection with *Bordetella pertussis*. Patients with abnormal vital signs (pulse ≥100 beats/min, respiration ≥24 breaths/min, temperature ≥100.4°F [38.0°C]) and examination findings consistent with pulmonary consolidation should be evaluated further for the diagnosis of pneumonia and treated appropriately, if confirmed. Pneumonia may present atypically in the elderly and in persons with chronic lung disease. Physicians must have a higher index of suspicion in these populations.

As some of the symptoms of bronchitis are caused by airway hyperreactivity, bronchodilator therapy has been shown in some studies to offer benefit in reducing symptoms. Antitussives, such as dextromethorphan and codeine, may have modest benefits in reducing the cough associated with this illness.

OTHER INFECTIONS OF THE UPPER RESPIRATORY TRACT

Rhinosinusitis

Rhinosinusitis is the inflammation/infection of the nasal mucosa and of one or more paranasal sinuses. Sinusitis occurs with obstruction of the normal drainage mechanism. It is traditionally subdivided into acute (symptoms lasting <4 weeks), subacute (symptoms lasting 4-12 weeks), chronic (symptoms lasting >12 weeks), and acute exacerbation of chronic sinusitis.

The signs and symptoms of rhinosinusitis are nonspecific and similar to other general upper respiratory tract infection symptoms. As most viral upper respiratory tract infections improve in 7 to 10 days, expert opinion suggests considering a diagnosis of bacterial rhinosinusitis after 7 days of symptoms in adults and 10 days in children. The diagnosis is suggested by the presence of purulent nasal discharge, maxillary tooth or facial pain, unilateral maxillary sinus tenderness, and worsening of symptoms after initial improvement.

Streptococcus pneumoniae and *Haemophilus influenzae* are the organisms most commonly responsible for acute bacterial sinusitis in adults; *S pneumoniae*,

H influenzae, and *Moraxella catarrhalis* are most common in children. In chronic sinusitis, the infecting organisms are variable, with a higher incidence of anaerobic organisms seen (eg, *Bacteroides*, *Peptostreptococcus*, and *Fusobacterium species*).

Treatment of acute sinusitis should be directed at the likely causative agents. Amoxicillin and trimethoprim-sulfamethoxazole are widely used first-line agents, typically for 10- to 14-day regimens. Second-line antibiotics, for those who fail to improve on the initial regimen or who have recurrent or severe disease, include amoxicillin-clavulanic acid, second- or third-generation cephalosporins (cefuroxime, cefaclor, cefprozil, and others), fluoroquinolones, or second-generation macrolides (azithromycin, clarithromycin). Adjunctive therapy with oral or topical decongestants may provide symptomatic relief. Topical decongestants should not be used for more than 3 days, to avoid the risk of rebound vasodilation with resultant worsening of symptoms. Nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen may provide symptomatic relief of pain and fever.

Pharyngitis

Pharyngitis is an inflammation or irritation of the pharynx and/or tonsils. In adults, the **vast majority of pharyngitis is viral.** It can also be bacterial or allergic in origin; trauma, toxins, and malignancy are rare causes. As most cases of pharyngitis in adults are benign and self-limited, a focus of the examination of a patient with symptoms of pharyngitis should be to rule out more serious conditions, such as epiglottitis or peritonsillar abscess, and to diagnose group A β-hemolytic *Streptococcus* (GAS) infection.

Pharyngitis occurs with much greater frequency in the pediatric population, with a peak incidence between 4 and 7 years of age. *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Arcanobacterium haemolyticus* are common causes of pharyngitis in teens and young adults. GAS causes 15% of all adult pharyngitis and approximately 30% of pediatric cases.

The cause of pharyngitis cannot always be distinguished based on history or examination. Sore throat associated with cough and rhinorrhea is more likely to be viral in origin. The presence of tonsillar exudates does not distinguish bacterial from viral causes, as GAS, Epstein-Barr virus (infectious mononucleosis), mycoplasma, chlamydia, and adenoviruses, among others, can all cause exudates. **Findings frequently associated with GAS infections include an abrupt onset of sore throat and fever, tonsillar and/or palatal petechiae, tender cervical adenopathy, and absence of cough.** GAS can also cause an erythematous, sandpaperlike (scarlatiniform) rash.

Infectious mononucleosis, caused by infection with Epstein-Barr virus, is extremely difficult to distinguish clinically from GAS infection. Exudative pharyngitis is prominent. Features suggestive of mononucleosis include retrocervical or generalized adenopathy and hepatosplenomegaly. Atypical lymphocytes can be seen on peripheral blood smear. The associated splenomegaly can be significant, as it predisposes to splenic rupture in response to trauma

(even minor trauma). A patient with splenomegaly from mononucleosis should be restricted from activities, such as sports participation, in which abdominal trauma may occur.

On examination, the **patency of the airway must be addressed first.** The presence of stridor, drooling, and a toxic appearance suggest epiglottitis. Patients with epiglottitis are sometimes seen leaning forward on their outstretched arms, the so-called tripod position. Patients with suspected epiglottitis need to be managed in a setting where the airway can be emergently secured, via intubation or cricothyroidotomy. Epiglottitis is a rare infection and is becoming even rarer, with near universal immunization for *H influenzae*, type B.

Swelling of the peritonsillar region, with the associated tonsil pushed toward the midline and with contralateral deviation of the uvula, is consistent with a peritonsillar abscess. This can be seen either as the initial complaint of sore throat, frequently with associated trismus (pain with chewing), or as a complication of streptococcal pharyngitis. Suspicion of peritonsillar abscess should prompt immediate referral for surgical drainage of the abscess.

The diagnosis of GAS infection can be made by rapid antigen testing or throat culture. **Rapid antigen tests** can be conducted in a few minutes in the office or emergency department setting. They are **highly specific but have a lower sensitivity than throat culture.** A positive rapid antigen test would prompt antibiotic treatment; a negative test should be followed by a throat culture. **Throat cultures are considered the gold standard** for diagnosis of GAS infections. Cultures can take 24 to 48 hours; this is acceptable in most instances, as the risk of complication from GAS infections is low if treatment is instituted within 10 days of onset of symptoms.

Complications from untreated GAS infections are rare, but include rheumatic fever, glomerulonephritis, toxic shock syndrome, peritonsillar abscess, meningitis, and bacteremia. Rheumatic fever, which may complicate up to 1 in 400 untreated cases of GAS pharyngitis, can cause permanent cardiac and neurologic sequelae. Glomerulonephritis results from antigen/antibody complex deposition in the glomeruli. **Poststreptococcal glomerulonephritis may occur whether or not the patient receives appropriate antibiotic treatment.**

Penicillin is the antibiotic of choice for GAS pharyngitis. Oral therapy requires a 10-day course of penicillin V. Intramuscular therapy of penicillin G benzathine for adults and children weighing more than 27 kg is 1.2 million units. Children who weigh less than 27 kg can receive 600,000 units of penicillin IM. In penicillin-allergic patients, treatment options include cephalosporins and macrolides.

INFECTIONS OF THE EAR

Otitis externa (OE) is an infection of the external auditory canal. Patients with OE complain of ear pain and, sometimes, itching. The pain from OE can be severe. Examination shows an inflamed, swollen, external ear canal, often

with exudates and discharge. Movement of the external ear is usually quite painful. The tympanic membrane may be uninvolved. The most common pathogens include staphylococci, streptococci, and other skin flora. Some cases have been associated with the use of swimming pools or hot tubs. This infection (swimmer's ear) is usually caused by *Pseudomonas aeruginosa*. Irrigation and administration of topical antibiotics, frequently combined with steroid, is usually successful. **Patients with diabetes mellitus are at risk for an invasive external otitis** (malignant OE) caused by *P aeruginosa*. Treatment for this condition involves surgical debridement of necrotic tissue and 4 to 6 weeks of IV antibiotics, if cranial bones are involved.

Otitis media (OM) is an infection of the middle ear seen primarily among preschool children, but occasionally in adults as well. Infection of the middle ear space, caused by upper respiratory tract pathogens, is promoted by obstruction to drainage through edematous, congested eustachian tubes. Viral infection with serous otitis may predispose to acute bacterial otitis media. Fever, ear pain, diminished hearing, vertigo, and tinnitus are common presenting symptoms. On examination, the tympanic membrane may appear red, but the presence of decreased membrane mobility or fluid behind the tympanic membrane are necessary for the diagnosis. *S pneumoniae, H influenzae*, and *M catarrhalis* are the most common bacterial pathogens. **Most cases of acute OM will resolve spontaneously.** Indications for treatment with antibiotics include prolonged, recurrent, or severe symptoms. Numerous antibiotics can be used for treatment. Amoxicillin remains the recommended initial therapy. Alternative treatments include amoxicillin-clavulanic acid, trimethoprim-sulfamethoxazole, or second- and third-generation cephalosporins. Complications are uncommon, but include mastoiditis, bacterial meningitis, brain abscess, and subdural empyema.

Comprehension Questions

19.1 A 25-year-old healthy woman presents with a cough productive of yellowish sputum for the past week. She has also had a runny nose and sore throat. Her 2-year-old son has been sick with a similar illness. In your office she is afebrile, has a normal ear, nose, and throat (ENT) examination and clear lungs. Which of the following statements is most accurate about this patient?

A. She most likely has a viral infection.
B. Because she has a cough productive of yellow sputum, she most likely has a bacterial infection.
C. This is probably the initial presentation of asthma.
D. This is probably related to a seasonal allergy.

19.2 A 40-year-old man presents with severe unilateral ear pain for the past 3 days. He swims daily at the YMCA for exercise. Which of the following are you most likely to find on examination?

A. A bulging tympanic membrane
B. Fever
C. An inflamed external ear canal
D. Tenderness over the mastoid process

19.3 An 18-year-old adolescent female comes to the office with a sore throat, fever, and fatigue. On examination, she has an exudative pharyngitis, bilateral cervical lymphadenopathy, and an enlarged spleen. Which of the following statements is most likely to be accurate?

A. There is a high likelihood that monospot testing will be positive.
B. She may return to playing for the school basketball team when her fever has resolved.
C. If not given antibiotics, she is at risk for developing rheumatic heart disease.
D. A complete blood count (CBC) is likely to show atypical neutrophils.

ANSWERS

19.1 **A.** This patient has an upper respiratory infection that is most likely viral. The color of her sputum does not necessarily indicate the presence of a bacterial infection. The absence of signs of consolidation on her pulmonary examination makes pneumonia unlikely. That her child has a similar illness also makes a contagious, viral infection more likely.

19.2 **C.** This patient has symptoms suggestive of "swimmer's ear," otitis externa, probably caused by *P aeruginosa*. The most common examination finding consistent with this is an inflamed external auditory canal. Other findings might be pain with movement of the external ear and exudates in the auditory canal.

19.3 **A.** Her symptoms and examination findings are consistent with infectious mononucleosis caused by Epstein-Barr virus. This infection often results in the finding of atypical lymphocytes (not neutrophils) on a CBC. As she has splenomegaly, she should be restricted from a sport, such as basketball, until her spleen is no longer palpable. Mononucleosis is a self-limiting disease.

Clinical Pearls

- The main concerns with pharyngitis are to rule out more serious conditions, such as epiglottitis or peritonsillar abscess, and to diagnose group A β-hemolytic streptococcal infections.
- Hepatosplenomegaly can be found in infectious mononucleosis infection.
- A tonsillopharyngeal exudate does not differentiate viral and bacterial causes.
- Tonsillopharyngeal/palatal petechiae are seen in GAS infections and infectious mononucleosis.

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Case 20

A 56-year-old man is brought to the emergency department complaining of chest discomfort for about 90 minutes. He has had occasional symptoms for a month, but it is worse today. Today's symptoms began while he was walking his dog and decreased slightly with rest, but have not resolved. He describes the feeling as a pressure sensation in the left substernal area of his chest associated with shortness of breath and mild diaphoresis. He does not have any radiation of the discomfort today, but has experienced radiation to the left upper extremity in the past. The patient denies any health problems, but his wife reports that he has not seen a physician in years. His wife made him come in because his younger brother had a heart attack 6 months ago. He is a vice president of a bank and lives with his wife and three daughters. He has smoked $1^1/_2$ packs of cigarettes per day for more than 30 years and denies drinking alcohol or any drug use.

On physical examination he is an anxious, obese gentleman who appears pale and has a moist brow. His temperature is 98.8°F (37.1°C), his pulse is 105 beats/min, his respirations is 18 breaths/min, his blood pressure is 190/95 mm Hg, his height is 74 in, and his weight is 250 lb. Cardiac examination reveals regular rhythm without murmur, but he has an S_4 gallop. Lungs are clear to auscultation. Neck is without carotid bruits or jugular venous distension. Abdomen is normal. He does have a right femoral bruit. Extremities reveal trace edema but no clubbing or cyanosis. He has 2+ pulses in radial and dorsal pedalis arteries. Rectal examination has no masses or tenderness with a normal prostate, and is guaiac negative.

- What is your most likely diagnosis?
- What is your next diagnostic step?
- What is the next step in therapy?

ANSWERS TO CASE 20:
Chest Pain

Summary: A 56-year-old obese man presents to the emergency department with chest discomfort. He has a pressure sensation in the left substernal area of his chest associated with shortness of breath and diaphoresis. His symptoms began with minimal exertion. The patient is without prior medical care. He has a family history of coronary artery disease (CAD) and a history of tobacco abuse. He is hypertensive and tachycardic. He has a cardiac gallop. Lower extremities have trace edema and a femoral bruit.

- **Most likely diagnosis:** Unstable angina pectoris; must rule out myocardial infarction (MI).

- **Next diagnostic step:**
  Initial studies in the emergency room: complete blood count (CBC), electrolytes, blood urea nitrogen (BUN), creatinine, prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR), glucose, 12-lead electrocardiography (ECG), and chest x-ray (CXR); markers of myocardial damage including creatine kinase (CK) and MB isoenzyme (CK-MB), troponin T and troponin I to be done stat and every 6 to 10 hours for three cycles. Oxygen saturation must be monitored, as well.

  Studies that can be performed later include: fasting lipids, liver function tests, magnesium, homocysteine level, urine drug screen, urinalysis, and myoglobin.

- **Next step in therapy: MONA** therapy: **M**orphine, **O**xygen, **N**itroglycerin, **A**spirin

  Morphine can achieve adequate analgesia which decreases levels of circulating catecholamines, thus reducing myocardial oxygen consumption. It must be initiated rapidly if nitroglycerin cannot alleviate the discomfort.
  Oxygen 2 to 4 L/min by nasal cannula; may be discontinued after 6 hours if oxygen saturation remains normal without other complications.
  Nitroglycerin must be given sublingually initially every 5 minutes for a total of three doses (in the absence of hypotension or contraindications such as sildenafil [Viagra] use), then advanced to IV or transdermal routes.
  Aspirin 325 mg should be chewed and swallowed (clopidogrel [Plavix] if allergy to aspirin exists).
  β-Adrenergic antagonist reduces myocardial damage and may limit infarct size.
  Glycoprotein (GP) IIb/IIIa inhibitors reduce end point of death or recurrent ischemia when given in addition to standard therapy for patients with high risk unstable angina or non–ST-elevation myocardial infarction treated with percutaneous coronary intervention, or who are refractory to prior treatment.

ANALYSIS

Objectives

1. Understand a diagnostic approach to chest pain and how to reduce potential damage to myocardium by implementing rapid evaluation.
2. Know the acute evaluation of chest pain and how to best implement the primary and secondary treatment of chest pain.
3. Identify the risks and the need to educate patients to reduce their risks.
4. Be familiar with the differential diagnosis of chest pain and how to best rule in and out the more life-threatening problems.

Considerations

This 56-year-old man has unstable angina with a variety of risk factors for CAD. All patients who present to primary care physicians with chest pain are immediate challenges. Most resources emphasize the life-threatening etiologies; however, the non–life-threatening etiologies are far more common in presentation. Physicians must master a cost-effective approach to diagnosing the various etiologies of chest pain, determining which patients warrant further evaluation, putting a large emphasis on thorough history and physical examination. The cause of this patient's symptoms must be determined as soon as possible. If the etiology is determined to be cardiac, there are medications and interventions that can dramatically reduce both morbidity and mortality. A complete history and physical examination can give information that can guide if and when other more expensive and invasive tests are necessary. The patient's most immediate problem is his acute symptoms. His anxiety will decrease slightly when he perceives that he is getting adequate care and information.

Nearly $1^1/_2$ million people in the United States experience a myocardial infarction each year. This is fatal approximately one-third of the time. However, there has been a continuous decline in the mortality rate over the past 3 decades because of a better understanding of the etiology and pathophysiology of myocardial infarction, and because of advances in therapeutic treatments.

The **first priority** is to obtain ECG and CXR, while giving medications to decrease the damage caused to his myocardium and simultaneously reducing his blood pressure. Nitroglycerin and β-adrenergic antagonists will begin achieving these goals. He will need constant monitoring and continuous telemetry. Oxygen needs to be continued as well. Before the ECG and CXR have been completed, aspirin, oxygen, nitroglycerin, morphine, and β-adrenergic antagonist should be given. The providers must assume cardiac etiology until it has been effectively ruled out to limit possible morbidity and mortality to the patient.

The labs previously listed need to be drawn, at which time IV access can be started in two places. The results of the tests will determine if the patient

has other risk factors in addition to his known hypertension, family history of CAD, tobacco abuse, and obesity. If he routinely walks his dog, his lifestyle contains at least minimal physical activity.

The changes seen in an ECG that are indicative of angina include ST-segment elevation or depression and/or T-wave inversion. Myocardial infarctions include these changes plus elevated CK-MB and/or troponin levels. Pathologic Q waves may also indicate cardiac pathology, but typically represent myocardial tissue necrosis from a completed infarction. When Q waves are present, the benefits of thrombolytic therapy are uncertain. **Not all myocardial infarctions will have ECG changes.** A normal ECG reduces the likelihood of myocardial infarction but does not rule out cardiac pathology. Any person with symptoms of angina who has a left bundle branch block (LBBB) on ECG must have serum cardiac enzymes drawn, because there is a high degree of correlation between LBBB and organic heart disease, especially CAD. LBBB can mask signs of myocardial pathology, as it can mimic both acute and chronic ischemic changes. All of the listed ECG changes have a differential diagnosis that includes myocardial infarction. The clinical picture is of utmost importance, again demonstrating the need for complete history and physical examination.

APPROACH TO
Chest Pain

DEFINITIONS

ANGINA PECTORIS: Severe pain around the heart caused by a relative deficiency of oxygen supply to the heart muscle.

MYOCARDIAL INFARCTION (MI): Cardiac muscle death caused by partial or complete occlusion of one or more of the coronary arteries.

NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION OF ANGINA:

Class I—Angina only with unusually strenuous activity

Class II—Angina with slightly more prolonged or slightly more vigorous activity than usual

Class III—Angina with usual daily activity

Class IV—Angina at rest

UNSTABLE ANGINA: Angina of new onset, angina at rest or with minimal exertion, or a crescendo pattern of angina with episodes of increasing frequency, severity, or duration.

CLINICAL APPROACH

Etiologies

Atherosclerosis leading to plaque rupture and then cascading to coronary artery thrombosis is the cause of an acute MI approximately 90% of the time, but **many different conditions can be the culprit for angina.** Coronary artery spasm, including cocaine-induced injury, can cause angina. Aortic dissection extending into a coronary artery will cause extensive damage. An embolus to a coronary artery can be caused by endocarditis, prosthetic heart valves, or myxoma. Embolism can also cause cerebral vascular accidents, increasing the extent of the initial evaluation that is warranted.

Chest pain or discomfort is one the most common complaints in both the outpatient and emergency setting. Determining the cause of such symptoms in a rapid fashion is of utmost importance. **If the patient is experiencing myocardial ischemia or infarction, time is myocardium.** Initial evaluation should be done within 10 minutes of presentation. Ischemic heart disease remains the leading cause of morbidity and mortality in the United States.

TREATMENT

Primary Treatment

All patients who rule in for myocardial infarction should receive aspirin and an antithrombotic treatment, if there are no contraindications. Aspirin and heparin reduce the risk of subsequent MI and cardiac death in patients with unstable angina. Studies present different recommendations for using clopidogrel in addition to aspirin and heparin. Current American College of Cardiology/American Heart Association recommendations advise withholding clopidogrel for 5 to 7 days before planned bypass surgery. It is reasonable to give clopidogrel 300 mg orally to patients with suspected acute coronary syndrome (ACS) (without ECG or cardiac marker changes) who are either allergic to or have gastrointestinal intolerance of aspirin.

Heparin usually should be continued for 48 hours or until angiography is performed. Patients suffering from unstable angina with ECG changes should also be given platelet glycoprotein IIb/IIIa receptor inhibitors because the composite risk of death, myocardial infarction, and recurrent ischemia is significantly reduced with these medications.

Nitroglycerin is best given IV initially because of the ability to achieve predictable blood levels rapidly. Once stabilized after 24 hours, the asymptomatic patient should be switched to a long-acting oral or transdermal nitrate. A β-adrenergic antagonist should also be given, unless contraindicated. The **combination of nitroglycerin and β-adrenergic antagonist reduces the risk**

of subsequent myocardial infarction. β-Adrenergic antagonists decreased mortality and reduced infarct size in many clinical trials.

Angiotensin-converting enzyme (ACE) inhibitors reduce short-term mortality when started within 24 hours of acute myocardial infarction. Postinfarction ACE inhibitors prevent left ventricular remodeling and recurrent ischemic events. It is reasonable to recommend their indefinite use in the absence of any contraindications. All trials with oral ACE inhibitors have shown benefit from their early use, including those in which early entry criteria included clinical suspicion of acute infarctions. Magnesium sulfate should be given if levels are low, as hypomagnesemia can increase the incidence of *torsade de pointes*-type ventricular tachycardia.

Despite the widespread use of calcium channel blockers both during and after myocardial ischemia, no evidence exists supporting any benefit when taking these medications. Rapid release, short-acting dihydropyridines (eg, nifedipine) are contraindicated because they increased mortality in multiple trials.

Patients who are asymptomatic after 48 hours of drug therapy can perform a modified Bruce protocol stress test. Patients who have a markedly positive stress test should be referred for angiography. There is some debate concerning when angiography should be done. One approach shows that an early invasive approach with angiography within 24 to 48 hours is beneficial, whereas others recommend a more conservative approach, doing angiography only if recurrent ischemia is present or a positive stress test is done. There is no clear consensus as to which approach is superior.

All patients admitted for angina or myocardial infarction should receive a reduced saturated fat and cholesterol diet. These patients may benefit from nutrition counselors to help them develop healthy lifestyle changes.

Secondary Treatment

Primary prevention of CAD must be encouraged for all patients. **Risk factors for CAD include diabetes mellitus, dyslipidemia, age, hypertension, tobacco abuse, family history of premature CAD, male gender, postmenopausal status, left ventricular hypertrophy, and homocystinemia** (Table 20–1). Modification of these risk factors has a direct link to reduce morbidity and mortality. Patient education is particularly important.

Aspirin, nitrates, and β-adrenergic antagonist have proven benefits for both primary and secondary treatment. Prolonged treatment with aspirin reduces risks for both CAD and cerebrovascular disease. β-Adrenergic antagonist reduces first-year mortality. If no adverse affects are experienced, patients should continue β-adrenergic antagonist 2 to 3 years or longer. Long-acting nitrates can treat angina symptoms.

Beta-hydroxy-beta-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) have documented a consistent decrease in the incidence of major adverse cardiovascular events when given within a few days after

Table 20–1 RISK FACTORS FOR CAUSES OF CHEST PAIN

RISK FACTOR	EVENT
Age/gender: male >40 y old	CAD
Hypertension	CAD and aortic dissection
Tobacco abuse	CAD, thromboembolism, aortic dissection, pneumothorax, and pneumonia
Diabetes mellitus	CAD
Cocaine use	MI
Hyperlipidemia Increasing TC, TG, LDL Decreasing HDL	MI
Left ventricular hypertrophy	MI
Family history of premature CAD	MI
Blunt trauma to chest	Pneumothorax, myocardial or pulmonary contusion, chest wall injury

Abbreviations: CAD, coronary artery disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MI, myocardial infarction; TC, total cholesterol; TG, triglyceride.

onset of ACS. There are few data on patients treated within 24 hours of the onset of symptoms. It is safe and feasible to start statin therapy early (within 24 hours) in patients; once started, continue statin therapy uninterrupted. The goal level for low-density lipoprotein (LDL) cholesterol in anyone with a history of CAD and high risk for future cardiac events is less than 70 mg/dL.

Hypertension must be treated using agents that reduce cardiac complications, as previously discussed. If further reduction is necessary, many medications treat hypertension and angina. Blood pressure and coronary pathology have a linear relationship; as blood pressure is reduced, the risk, morbidity, and mortality of cardiac disease are also reduced. Agents used often depend on a patient's comorbid conditions.

Physical activity is an important component of lifestyle change. Recommendation of a minimum goal of 30 minutes of exercise on most days should be given to all patients. Weight management is also encouraged, but often requires numerous interventions. A minimum of a 5% reduction in weight will provide benefits to the patient. Body mass index needs to become part of the vital signs examined every visit.

CLINICAL PRESENTATION

The history should focus on onset and evolution of the chest pain. The cardinal features of all chief complaints should be followed, paying attention to patient's description of the pain/discomfort, location, radiation of pain, quality of pain, quantity of pain, duration, associating factors, and aggravating and/or alleviating factors (Table 20–2). **Many people do not describe angina as chest pain.** It is more effective to ask the patient to describe the discomfort. Some describe it as pressure, squeezing, crushing, or smothering. Some may use a "Levine sign," a fist held firmly against the chest. The discomfort is usually central and substernal. It may radiate to the jaw, shoulder, arm, or hand; usually to the left side. Cardiogenic nausea and vomiting are associated with larger MIs.

The relationship of the symptoms to exertion is very important. Exertion, emotional stress, or other situations that either increase myocardial oxygen demand or decrease oxygen supply can increase symptoms. **Angina usually responds promptly to measures that reduce myocardial oxygen demand,** such as rest. Pain typically resolves in less than 5 minutes. If angina persists for longer than 20 to 30 minutes, a myocardial infarction is more likely. In this setting, hospitalization and further evaluation are warranted.

The targeted history in patients with angina needs to ascertain whether the patient has had prior episodes of myocardial ischemia (stable or unstable angina, MI, interventions such as bypass surgery or angioplasty). Evaluation of the patient's complaints should focus on chest discomfort, associated symptoms, gender and age-related differences in presentation, hypertension, diabetes mellitus, possibility of aortic dissection, risk of bleeding, and clinical cerebrovascular disease (amaurosis fugax, face/limb weakness or clumsiness, face/limb numbness or sensory loss, ataxia, or vertigo).

The physical examination needs to concentrate on evidence that supports or disproves a diagnosis of cardiovascular disease. General appearance and vital signs can reveal much about the patient and the patient's stability. Hypertension, evidence of elevated lipids, changes consistent with diabetes mellitus, and signs of peripheral vascular disease all increase the risk of CAD.

Funduscopic examination can show signs of chronic hypertension or diabetes mellitus. All blood vessels must be auscultated for bruits, a direct sign of atherosclerotic disease. Diminished peripheral pulses are also a sign of atherosclerotic disease. Signs of heart failure include pulmonary edema, rales, jugular venous distension, and hepatojugular reflux. New gallops or murmurs can signal myocardial ischemia. Shallow, painful breathing suggests chest pain with a pleural cause. Asymmetric expansion of the chest with unilateral hyperresonance to percussion and diminished breath sounds are indicative of a possible pneumothorax.

The cardiac examination requires careful evaluation. **Unequal carotid pulses or upper extremity pulses can indicate aortic dissection, but most patients with**

Table 20–2 DIFFERENTIAL DIAGNOSIS OF CHEST PAIN

DISORDER	SYMPTOMS/FINDINGS	STUDIES
Angina	Substernal pressure for duration <30 min Radiation to arm, neck, jaw ± dyspnea, N/V, diaphoresis ↑ with exertion; ↓ with rest and NTG	ECG, CXR, serum values
MI	Anginal symptoms but duration >30 min	ECG, CXR, serum values
Pericarditis	Sharp pain radiates to trapezius ↑ with respiration; ↓ with sitting forward	Friction rub, ECG, ± pericardial effusion
Aortic dissection	Sudden onset of tearing pain with radiation to back	CXR, widened mediastinum CT, TEE, MRI
Heart failure	Exertional chest pain and dyspnea (uncommon cause of angina, but often patients may also have CAD)	CXR, displaced apical impulse, edema (pulmonary, lower extremities), JVD, cardiac gallop, murmurs
Pneumonia	Dyspnea, fever, and cough; pleuritic pain	CXR, egophony, dullness to percussion
Pneumothorax	Unilateral sharp pleuritic pain of sudden onset, CXR findings	Unilateral ↓ breath sounds and/or hyperresonance
Pulmonary embolism	Sudden onset of pleuritic pain, tachycardia, tachypnea, hypoxemia	D-dimer, V/Q scan, CT chest, pulmonary angiogram
Gastroesophageal reflux	Burning epigastric/substernal pain, acid taste in mouth, ↑ with meals; ↓ with PPIs or antacids	Endoscopy, esophageal pH probe
Peptic ulcer disease	Epigastric pain ↓ with antacids and PPIs	Endoscopy *Helicobacter pylori* test
Pancreatitis	Severe epigastric and back pain	↑ amylase and lipase, abdominal CT

(*Continued*)

Table 20–2 DIFFERENTIAL DIAGNOSIS OF CHEST PAIN (CONTINUED)

DISORDER	SYMPTOMS/FINDINGS	STUDIES
Costochondritis	Localized pain that is easily reproducible, tender to palpation	Tenderness to palpation
Anxiety	"Tightness" sensation of chest, SOB, tachycardia	Ask screening questions for anxiety and panic
Herpes zoster	Pain often presents prior to rash	Unilateral pain in dermatomal distribution

Abbreviations: ↓, decreasing; ↑, increasing; CAD, coronary artery disease; CT, computed tomography; CXR, chest x-ray; ECG, electrocardiogram; JVD, jugular venous distension; MI, myocardial infarction; MRI, magnetic resonance imaging; NTG, nitroglycerin; N/V, nausea and vomiting; PPI, proton pump inhibitor; SOB, shortness of breath; TEE, transesophageal echocardiogram.

dissection will not have pulse deficit. The murmur of aortic stenosis can be significant, as aortic stenosis can present with angina, which can then lead to syncope and heart failure.

The patient's chest wall should be palpated. If this examination reproduces the chest pain, costochondritis becomes more likely. **Musculoskeletal causes of chest pain are the most common etiology in an outpatient setting.** Abdominal examination is also important, as gastrointestinal etiology is the second most common culprit for chest pain in an outpatient setting. Careful examination of both upper quadrants and epigastric area must be done. The abdominal aorta warrants careful examination.

Comprehension Questions

20.1 A 58-year-old man presents to his physician for follow-up of his hypertension and hyperlipidemia. He also reports chest pain and feeling short of breath after climbing two flights of stairs or walking three to four blocks. The symptoms resolve after several minutes of rest. Which of the following drugs is contraindicated as a first-line agent in the treatment of this patient's new condition?

A. Labetalol
B. Nitroglycerin
C. Enalapril
D. Nifedipine
E. Aspirin

20.2 A 45-year-old man complains of vague chest discomfort associated with dyspnea. This pain increases with exertion. He is also a "nervous" person and is prone to anxiety. An abnormality of which of the following is most specific for chest pain of cardiac etiology?

A. Chest radiograph
B. Serum lipid panel
C. 12 lead ECG
D. Pulse oximetry

20.3 Which of the following ECG changes makes the determination of acute MI the most difficult?

A. Q wave
B. ST-segment elevation
C. Left bundle branch block
D. First-degree atrioventricular block
E. T-wave inversion

20.4 A 64-year-old woman with a history of hypertension and angina pectoris presents with chest pain for the last 3 hours. She describes the pain as "sharp," it is worse when she inhales deeply, and it is not relieved by sublingual nitroglycerin. Her ECG shows ST elevation in most leads. Which of the following is the most likely diagnosis in this patient?

A. Unstable angina pectoris
B. Myocardial infarction
C. Aortic dissection
D. Congestive heart failure
E. Pericarditis

ANSWERS

20.1 **D.** This patient has new onset of angina. Rapid release, short-acting dihydropyridines (nifedipine) are contraindicated because they increased mortality in multiple trials. Beta-blocking agents are the agents of choice since they increase survival; nitroglycerin helps to abate chest pain, but have not been shown to impact survival.

20.2 **C.** The clinical history is the most significant single factor in identifying cardiac from other types of chest pain. The next best modality is the 12 lead ECG.

20.3 **C.** The changes of left bundle branch block make the determination of an acute MI by an ECG extremely difficult. In these patients, it is particularly important to obtain serum markers of myocardial damage.

20.4 **E.** This patient likely has pericarditis. The pain is described as sharp in nature rather than dull, aching, pressure. The pain is exacerbated by inspiration, and finally there is global ST-segment elevation noted on the ECG.

Clinical Pearls

- Angina pectoris is the most frequent symptom of intermittent ischemia.
- Targeted history and physical examinations of patients with angina is vital to expedite proper diagnosis and treatment of patients. The patient's description of their discomfort is key; history must be given attention because it is the most important diagnostic factor.
- Physical examination may be normal in many patients with angina.
- Aspirin, nitrates, β-adrenergic antagonists, and statins are the backbone in treatment and prevention of myocardial pathology, having proven benefit for both primary and secondary treatment.
- Time is myocardium. Initial diagnosis and treatment must be done as soon as possible.
- Be mindful of polypharmacy, as many drugs have side effects that can exacerbate myocardial damage.

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Case 21

A 46-year-old woman presents to the clinic for the first time, complaining of decreased urinary output for 5 months with a foamy appearance. She also complains of swelling in both legs and nonbloody, nonbilious emesis a few times a week. She was diagnosed with diabetes 10 years ago and has been taking insulin for 2 years. She does not check her sugars at home because she does not like to stick herself. When asked about her diet she states that she eats the best she can for what she can afford but often has very little appetite. The patient last saw her physician 8 months ago and insulin is her only medication. On examination, the patient is an obese woman. Her temperature is 99°F (37.2°C), her heart rate is 108 beats/min, her blood pressure is 198/105 mm Hg, her respiration is 19 breaths/min, and her oxygen saturation is 94% on room air. A head, ears, eyes, nose, and throat (HEENT) examination reveals periorbital edema. Her skin is hyperpigmented on both lower extremities. Her heart is tachycardic with an S_1, S_2, S_4 gallop auscultated with no murmur or rub. When palpating the heart's point of maximal impulse (PMI), it is lateral to the left midclavicular line. There are vesicular breath sounds in both lungs throughout. Her neck reveals no jugular venous distension and there are no carotid bruits. Her abdomen is nontender, with no bruits or masses palpated. The lower extremities reveal pitting pretibial edema with a pit recovery time less than 40 seconds. Laboratory studies in your office include a urinalysis showing hyaline casts, 3+ proteinuria, and glucose, but negative for ketones. Her hemoglobin is 10.9 g/dL and her hematocrit is 32% with a mean corpuscular volume (MCV) of 82.3 g/dL.

- What is the most likely diagnosis?
- What is your next diagnostic step?
- What is the next step in therapy?

ANSWERS TO CASE 21:
Chronic Kidney Disease

Summary: This is a 46-year-old woman with chronic kidney disease (CKD). She has a history of uncontrolled diabetes and currently has uncontrolled hypertension. She presents with periorbital edema, long-standing lower-extremity edema, an S_4 and displaced PMI, and central obesity. The urinalysis shows hyaline casts, 3+ proteinuria and glucose, negative ketones, and hemoglobin 10.9 g/dL with an MCV of 82.3 g/dL.

- **Most likely diagnosis:** Acute worsening of chronic kidney disease
- **Next diagnostic step:** Measurement of serum electrolytes, blood urea nitrogen (BUN), and creatinine; imaging of the kidneys
- **Next step in therapy:** Further history to identify and remove any offending agents (such as nonsteroidal anti-inflammatory drugs [NSAIDs]), and control of blood pressure and diabetes; may require dialysis if she develops complications such as pulmonary edema, severe hyperkalemia, or anuria

ANALYSIS

Objectives

1. Know the risks for developing CKD.
2. Learn to evaluate for CKD.
3. Be familiar with the management of CKD.
4. Recognize the complications associated with CKD.

Considerations

This 46-year-old patient presents with a concerning symptom of a decrease in urination with a change in the appearance of the urine. The most immediate concern is how often she is urinating and to what degree is she urinating less. A significant reduction requires immediate evaluation of creatinine function and volume status. Volume status is assessed by skin turgor, mucous membranes, specific gravity in the urinalysis, and orthostatic blood pressure, which also measures heart rate in the lying, sitting, and standing positions. A low volume status with an elevated creatinine requires that the patient be given IV fluids to see if there can be any recovery of kidney function. The patient's uncontrolled diabetes and hypertension predispose her to kidney damage. Another common offender is a patient with this history who is taking NSAIDs. This will increase the patient's already high risk of damage.

With chronic kidney failure, patients are often able to compensate for the metabolic imbalances that occur such as hyper- or hyponatremia, hyperkalemia, elevated uric acid levels, and metabolic acidosis. Patients also experience hyperparathyroidism. Significantly elevated potassium levels require treatment with sodium polystyrene sulfonate (Kayexalate), insulin with glucose, and retention enemas, depending on the degree of elevation. When the patient is no longer compensating, there are symptoms of pulmonary edema, which include shortness of breath, lower-extremity edema, jugular venous distension, and abnormal lung sounds (rales). This patient was compensating and mostly demonstrated the result of a hypoalbuminemic state from the loss of protein in the urine. She had lower-extremity edema with a long pit time that reflected her low albumin state. Her occasional emesis reflects high levels of urea and other toxins. Persistent emesis mandates treatment. Her normocytic anemia was the result of reduced erythropoietin from the kidneys. In this setting, treatment with exogenous erythropoietin improves prognosis for cardiovascular mortality. The hyaline casts reflect the long-standing damage to the kidneys.

Increasing the patient's chance of improved kidney function requires glucose and blood pressure control, removing offenders such as NSAIDs and diuretics (if allowable), maintaining normal volume status (which is difficult with a low albumin state), and adding agents that both treat blood pressure and improve kidney and cardiovascular function such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs). CKD itself is a cardiovascular risk factor. Patients are more likely to die from cardiovascular disease than to develop end-stage renal disease (ESRD) requiring dialysis. The patient's gross proteinuria of 3+ reflects her high risk for cardiovascular disease.

APPROACH TO
Chronic Kidney Disease

DEFINITIONS

CKD: A spectrum of processes associated with abnormal kidney function and progressive decline in glomerular filtration rate (GFR).

ESRD: The irreversible loss of kidney function such that the patient is permanently dependent on renal replacement therapy (dialysis or transplantation). Also defined as a GFR of less than 15 mL/min.

CLINICAL APPROACH

Etiologies

Chronic kidney disease is becoming more common in the United States. **The most common etiologies are diabetes, hypertension, and glomerulonephritis**. Diabetic kidney disease occurs in 30% to 40% of type I diabetics, in 25% of type II diabetics, and in 24% of hypertensive patients. Within the diabetic patient population, 20% to 60% have hypertension. Many patients present at a later stage of CKD and it is then difficult to determine the etiology.

Evaluation

The Kidney Disease Outcomes Quality Initiative (KDOQI) from the National Kidney Foundation (NKF) recommends both a serum creatinine (Cr) to estimate GFR and random urinalysis for albuminuria in those groups at risk for chronic kidney disease (CKD). The stage of CKD is based on GFR, which can be estimated with a random Cr level calculated with one of two commonly used equations:

Modification of Diet in Renal Disease (MDRD) equation:

$$\text{GFR (mL/min/1.73 m}^2) = 186 \times (\text{Scr})^{-1.54} \times (\text{age})^{-0.203} \times (0.742, \text{if woman}) \times (1.210, \text{if black})$$

Cockcroft-Gault equation:

$$\text{Ccr (mL/min)} = ((140 - \text{age}) \times \text{weight}/72 \times \text{Scr}) \times (0.85, \text{if female})$$

(Scr = serum creatinine concentration; Ccr = creatinine clearance).

A normal GFR for a woman is between 100 and 120 mL/min. Stage 1 of CKD correlates with a GFR more than 90 mL/min; stage 2 correlates with a GFR of 60 to 89 mL/min; stage 3 correlates with a GFR of 30 to 59 mL/min; stage 4 correlates with a GFR of 15 to 29 mL/min; and stage 5 correlates with a GFR less than 15 mL/min or dialysis. The Cockcroft-Gault equation is preferred for older patients. A 24-hour urine collection is recommended for persons with extremes of age and weight, malnutrition, skeletal muscle disease, paraplegia or quadriplegia, or a vegetarian diet.

The evaluation in all patients with CKD includes renal imaging and microscopic evaluation of urine. Treatment may be more successful in patients with normal-size kidneys. Small kidneys show irreversible disease. Asymmetry suggests renovascular disease. Evidence of proteinuria or microalbuminuria should be evaluated in all patients with CKD. If the urine dipstick does not reveal gross proteinuria, a sample should be sent to evaluate for microalbumin. A test is positive if there is more than 30 mg of microalbumin per gram Cr. It is recommended in the case of less than 200 mg of protein per gram Cr that the test be repeated yearly. Any patient with more than 200 mg of protein per gram Cr will need diagnostic evaluation and treatment. The protein-to-creatinine

ratio in an early morning random urine sample may be used instead of a 24-hour urine protein excretion.

Underlying causes may be ascertained through clinical presentation, symptomatology, and past medical and family history. Some common lab studies include C3, C4, hepatitis panel, HIV test, protein and urine electrophoresis for those patients older than age 40, hemoglobin A_{1c}, fasting blood sugar, and analysis of urine sediment. Renal biopsy is indicated in patients with unknown etiology after history and lab evaluation, if parenchymal disease is suspected, or if treatment or prognosis will be based on the biopsy.

Management

Managing CKD includes treatment of reversible causes. Hypovolemia, hypotension, infection leading to sepsis, and drugs that lower the GFR all reduce renal perfusion. History and physical examination allow for this diagnosis, and a trial of fluids may improve kidney function. Drugs such as NSAIDs, aminoglycosides at full strength, and radiographic contrast material can affect kidney function. Urinary tract obstruction, commonly caused by prostate enlargement in elderly men, is a potentially reversible cause.

Goals of treatment include a blood pressure less than 130/80 mm Hg and a reduction of protein excretion to less than 500 to 1000 mg/d (or at least 60% of the baseline value). KDOQI guidelines recommend starting with an ACE inhibitor or an ARB, followed by a diuretic if the blood pressure goal is not achieved. Additional medications are diltiazem, verapamil, or a β-blocker. If the proteinuria goal continues to be unmet after achieving blood pressure control, add either the ACE inhibitor or an ARB. Combining both an ACE inhibitor and an ARB requires reevaluating the potassium and Cr 3 to 5 days after initiation, because of its potential for worsening function. Nonproteinuric renal disease strictly requires blood pressure control.

Other treatments may be beneficial in CKD. Dietary protein restrictions of 0.8 to 1.0 mg/kg/d may be beneficial. Hyperlipidemia should be treated with a goal low-density lipoprotein (LDL) of less than 100 mg/dL, and some say the goal should be less than 70 mg/dL because CRF is a cardiovascular equivalent. The volume overload associated with CRF responds well to sodium restriction and loop diuretics. This lowers the intraglomerular pressure. Hyperkalemia may be prevented by a low-potassium diet and avoiding drugs such as NSAIDs and, sometimes, ACE inhibitors. Metabolic acidosis may be treated with sodium bicarbonate, with a goal to maintain a concentration of 22 mEq/L. Dietary phosphate restriction may limit the development of secondary hyperparathyroidism in these patients.

When the GFR is below 25 to 30 mL/min, oral phosphate binders are usually required. Caution is used when treating hyperphosphatemia in stages 3 to 5 CKD. It is suggested that calcium intake not exceed 2000 mg/d, as this may contribute to cardiovascular disease.

The KDOQI guidelines suggest evaluation of anemia with a hemoglobin less than 11 g/dL in premenopausal women and prepubertal patients, and less than 12 g/dL in adult men and postmenopausal women. This should include evaluation for nonrenal causes of anemia. Treating patients with CKD with erythropoietin before they develop ESRD may reduce symptoms of anemia, show cardiovascular improvement, and possibly decrease mortality. Ultimately, the patient that is going toward ESRD must be identified and adequately prepared for renal replacement therapy. It is recommended that patients with a creatinine more than 1.2 mg/dL in women and more than 1.5 mg/dL in men be referred to a nephrologist for evaluation and recommendations.

Comprehension Questions

21.1 A 56-year-old man with known CKD presents with a 3-day history of shortness of breath and rapid weight gain. On examination you are able to auscultate an S_3, hear crackles at the bases, and see moderate jugular venous distension (JVD). Which of the following is your next step in evaluation?

A. Perform an echocardiogram.
B. Order a chest x-ray.
C. Measure a Cr to calculate GFR.
D. Check for cardiac enzymes.

21.2 A 39-year-old woman with multiple medical problems has been noted to have progressively worsening renal insufficiency. Which of the following measures is most important in the prevention of end stage renal disease?

A. Tobacco cessation
B. Triglyceride control
C. Glycemic control
D. Weight control
E. Dietary sodium restriction

21.3 A 72-year-old man, with a long history of hypertension, presents to the emergency department complaining of a 2-day history of emesis and 36 hours of no urination. On examination, the abdomen is firm and tender, and the prostate is enlarged. His serum creatinine level is is 3.4 mg/dL. Which the following is the best next step?

A. Give him IV fluids and see if he begins to make urine.
B. Perform a renal ultrasound in the emergency department.
C. Maintain tight control of his blood pressure.
D. Place an indwelling Foley catheter.

21.4 A 45-year-old woman with type II diabetes presents to the clinic with decreased vision in the left eye for 1 year, 1+ proteinuria, a baseline Cr of 1.6 mg/dL, an LDL of 135 mg/dL, blood pressure of 145/92 mm Hg, and occasional chest pain for the past 2 months. Which of the following is the best medication to start the patient on at this time?

A. ACE inhibitor
B. β-Blocker
C. Oral nitrate
D. Thiazide diuretic

ANSWERS

21.1 **B.** The patient has CKD with volume overload as evidenced by symptoms and physical examination. A simple first step is to do a chest x-ray to confirm what you already suspect—pulmonary edema. After initiating furosemide (Lasix), the chest x-ray may be repeated to see to what degree the diuresis has improved the overload. Cardiac workup is also indicated but would not be the first test done.

21.2 **C.** Optimal control of high blood pressure, acidosis, volume depletion, and cholesterol are all important to prevent worsening renal function. Diabetes is a leading cause of end stage renal disease. Tight glycemic control can prevent the microvascular complications of diabetes such as diabetic nephropathy, though it has not been shown to decrease significantly the occurrence of macrovascular complications of diabetes such as CAD or PVD. Treating secondary hyperparathyroidism prevents complications such as renal osteodystrophy. The patient's weight does not impact on renal function substantially. Smoking has numerous health risks but does not tend to impact kidney function directly; nevertheless, its effect on cardiovascular system may impact on the kidneys.

21.3 **D.** The patient has an enlarged prostate that has caused urinary obstruction and potentially reversible renal failure, depending on at which point the obstruction is resolved. Placing the Foley catheter will usually allow for significant reversal of an elevated Cr. Following catheter placement, the urine output needs to be carefully monitored and the Cr repeated later. Another clue is the tense lower abdomen that is caused by a very enlarged bladder. It is especially important to rely on clinical examination skills in elderly patients who have less-than-optimal communication skills as a consequence of dementia or who have a history of stroke when evaluating for a cause.

21.4 **A.** ACE inhibitors would help in hypertension treatment and to protect renal function in this patient. Both diabetes and CKD are known to be cardiovascular risk equivalents. Other factors, such as uncontrolled blood pressure and cholesterol, add to the patient's high risk, which is why it is so important for all diabetics and CKD patients to improve all modifiable risk factors. The goals become much more stringent when looking at these two groups of patients.

Clinical Pearls

- Small kidneys on imaging usually reflect irreversible disease. Small kidneys should rarely be biopsied, as the result of the biopsy usually will not alter the treatment or prognosis of the condition.
- Calculation of the estimated GFR is an important process as, especially in older persons, a seemingly normal serum creatinine could reflect a significant reduction in GFR.

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Case 22

A 25-year-old woman presents to the office with a 1-week history of vaginal discharge. She describes the discharge as being green-yellow in color with a bad odor. She has never had this type of discharge in the past. She complains of increased vaginal soreness and discharge after she has intercourse. She denies any itching, abdominal pain, nausea, vomiting, fever, chills, or sweats. She is currently sexually active and is using an intrauterine device (IUD) as her contraceptive method. She has been with one male partner for the past 3 months and he has no symptoms. She does state that she first had intercourse at age 15 and has had multiple sexual partners. She had a chlamydial infection 2 years ago that was treated with oral antibiotics. Her last menstrual period was 2 weeks ago and was normal. She also denies any recent antibiotic treatment. On examination, she is afebrile, has normal vital signs, and appears to be in no acute distress. Her general physical examination is normal. On pelvic examination, she has normal external genitalia. She has a small amount of frothy, homogenous green-gray discharge at the introitus. The cervix has a "strawberry"-red appearance with a slight amount of discharge noted in the os. The IUD string is in place. *Chlamydia* and gonorrhea specimens are obtained from the os and a sample of the vaginal discharge is collected for microscopic evaluation. Bimanual examination shows no cervical motion tenderness, and a normal uterus and adnexa.

- What organism is the most likely cause of her symptoms?
- What would you expect to see on microscopic examination of the vaginal discharge?
- What is the recommended treatment for this infection?

ANSWERS TO CASE 22:
Vaginitis

Summary: A 25-year-old woman presents with a foul-smelling vaginal discharge. She has a greenish, frothy discharge and a "strawberry cervix" noted on examination.

- **Organism most likely to cause this infection:** *Trichomonas vaginalis*.
- **Expected microscopic examination findings:** Motile, flagellated trichomonads, and many white blood cells.
- **Recommended treatment:** Metronidazole 2 g by mouth in a single dose for both the patient and her sexual partner. Metronidazole 500 mg twice a day for a week is an alternate regimen.

ANALYSIS

Objectives

1. Be able to differentiate among common presentations of vaginitis on the basis of clinical information and laboratory testing.
2. Know the current guidelines for treatment of the various etiologies of vaginitis.

Considerations

Women with vaginitis may present with a variety of symptoms, including vaginal discharge, itching, odor, and dysuria. There are many potential causes of vaginitis, including sexually transmitted pathogens and overgrowth of organisms found in the normal vaginal flora. Common among the causes of vaginitis are *Candida albicans*, *Trichomonas vaginalis*, and *Gardnerella vaginalis*.

Certain historical information may lead a clinician to suspect a specific cause of vaginitis in a given patient. For example, a history of recent antibiotic use may predispose to a *Candida* vaginitis, as the antibiotic may alter the normal vaginal flora and allow the overgrowth of a fungal organism. Women with diabetes mellitus are also more predisposed to developing yeast infections. A history of multiple sexual partners may raise the likelihood of a sexually transmitted infection, such as trichomoniasis.

The patient's symptoms and signs may also suggest a specific organism as the cause of her vaginitis. Fungal infections tend to have thick discharge and cause significant pruritus. The discharge of bacterial vaginosis is often thinner

and patients complain of a "fishy" odor. *Trichomonas* produces a discharge that is usually frothy and the patient's cervix is frequently very erythematous.

The key test to determining the cause of vaginal discharge, which guides the specific treatment, is microscopic examination of the discharge. A sample of the discharge is examined both as a "wet mount" (ie, mixed with a small amount of normal saline) and as a "KOH prep" (ie, mixed with a small amount of 10% potassium hydroxide). On wet mount, the examiner can evaluate the normal epithelial cells and look for white blood cells, red blood cells, clue cells, and motile trichomonads. The hyphae or pseudohyphae of *Candida* are best seen on KOH prep.

APPROACH TO
Vaginal Infections

DEFINITIONS

BACTERIAL VAGINOSIS: Condition of excessive anaerobic bacteria in the vagina, leading to a discharge that is alkaline.

CANDIDA VULVOVAGINITIS: Vaginal and/or vulvar infection caused by *Candida* species, usually with heterogenous discharge and inflammation.

TRICHOMONAS VAGINITIS: Infection of the vagina caused by the protozoa *Trichomonas vaginalis*, usually associated with a frothy green discharge and intense inflammatory response.

CLINICAL APPROACH

ETIOLOGIES

Vulvovaginal Candidiasis

This infection is typically caused by *C albicans*, although other species are occasionally identified. **More than 75% of women have at least one episode during their lifetime.** The presenting symptom is a thick, whitish discharge that has no odor and the patient complains of significant pruritus of the external and internal genitalia. On physical examination, the vaginal area can be edematous with erythema present. The discharge has a pH between 4.0 and 5.0. The diagnosis is confirmed by wet mount or KOH preparation showing budding yeast or pseudohyphae. **Fungal cultures are not needed to confirm the diagnosis,** but they are useful if the infection recurs or is unresponsive to

treatment. Numerous treatment options are available for patients with vulvovaginal candidiasis, including over-the-counter and prescription medications. Uncomplicated candidiasis can be treated effectively with short-term intravaginal preparations (creams or vaginal suppositories) or single-dose oral therapies (fluconazole 150 mg). Treatment of complicated or recurrent infection should begin with an intensive regimen for 10 to 14 days followed by 6 months of maintenance therapy to reduce the likelihood of recurrence. Treatment of sexual partners is not indicated unless symptomatic (eg, man partners with balanitis).

Trichomoniasis

This infection is caused by the protozoan *T vaginalis* and is classified as a sexually transmitted disease. The incubation period is 3 to 21 days after exposure. **Certain factors predispose to infection, such as multiple sexual partners, pregnancy, and menopause.** The presenting complaint is copious amounts of a thin, frothy, green-yellow or gray malodorous vaginal discharge. Women can also have vaginal soreness or dyspareunia. Symptoms may start or be exacerbated during the time of their menses. Vaginal examination may reveal that the **cervix has a "strawberry" appearance** (red and inflamed with punctuations) or that redness of the vagina and perineum is present. Microscopically, the **wet mount preparation can demonstrate motile trichomonads,** although cultures may be necessary because of the significant number of false-negative results. The recommended treatment for trichomoniasis is oral metronidazole, given in a single, 2-g oral dose or 1-week regimen of 500 mg twice a day to both the patient and her sexual partner. **It is important to screen for other sexually transmitted diseases (STDs) and to remember to treat the partner to ensure better cure rates.**

Bacterial Vaginosis

Bacterial vaginosis (BV) arises when normal vaginal bacteria are replaced with an **overgrowth of anaerobic bacteria and *G vaginalis*.** Although not an STD, it is associated with having multiple sexual partners. **Diagnosis can be based on the presence of three of four clinical criteria:** (1) a thin, homogenous vaginal discharge; (2) a vaginal pH more than 4.5; (3) a positive KOH "whiff" test (a fishy odor present after the addition of 10% KOH to a sample of the discharge); and (4) the presence of clue cells in a wet mount preparation (Figure 22–1). Culture is generally not needed. Treatment options include both oral and topical vaginal preparations of metronidazole or clindamycin. There are no advantages to any of these regimens with regard to cure rates or recurrence, although patients do report more satisfaction with the vaginal preparations. **Treatment of BV in asymptomatic pregnant women may reduce the incidence of preterm delivery.** Treatment of sexual partners is not necessary and does not reduce the risk of recurrent infection.

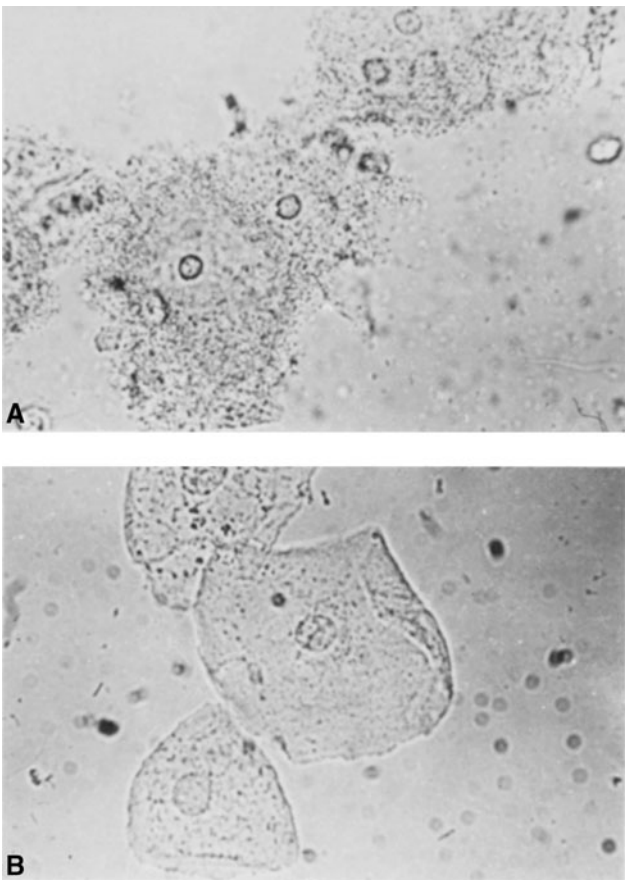

Figure 22–1. Bacterial vaginosis. (A) "Clue cells." (B) Normal epithelium. *Reproduced with permission from Kasper DL, Braunwauld E, Fauci A, et al.* Harrison's Principles of Internal Medicine. *16th ed. New York, NY: McGraw-Hill; 2005:767.*

Mucopurulent Cervicitis

This infection is characterized by purulent or mucopurulent discharge from the endocervix, which may be associated with vaginal discharge and/or cervical bleeding. The diagnostic evaluation should include testing for *Chlamydia trachomatis* and *Neisseria gonorrhoeae*, although the etiologic agent is not always found. Absence of symptoms should not prevent additional evaluation and treatment, as **approximately 50% of gonococcal infections and 70% of chlamydial infections are asymptomatic in women.** The gold standard for establishing

the diagnosis is a culture of the cervical discharge. **Empiric treatment should be considered in areas of high prevalence of infection or if follow-up is unlikely.** The treatment recommendation for gonorrhea is ceftriaxone 125 mg intramuscularly. Because of the growing problem of antibiotic resistance, quinolone antibiotics (ciprofloxacin, ofloxacin) are no longer recommended for treatment of gonorrhea. The recommended treatment for *Chlamydia* infections is doxycycline 100 mg orally twice daily for 7 days or azithromycin in a single 1-g oral dose when compliance is a concern. Typical treatment regimens will cover for both gonorrhea and chlamydia and the treatment of sexual partners is advised.

Pelvic Inflammatory Disease

Pelvic inflammatory disease (PID) is defined as inflammation of the upper genital tract, including pelvic peritonitis, endometritis, salpingitis, and tuboovarian abscess caused by infection with gonorrhea, *Chlamydia*, or vaginal and bowel flora. **Lower abdominal tenderness with both adnexal and cervical motion tenderness without other explanation of illness is enough to diagnose PID.** Other criteria that enhance the specificity of the diagnosis include temperature more than 101°F, abnormal cervical or vaginal discharge, elevated sedimentation rate, elevated C-reactive protein, and cervical infection with gonorrhea or *Chlamydia*. Definitive diagnosis rests on techniques that are not generally used or readily available to make the diagnosis, such as laparoscopic findings consistent with PID, endometrial biopsy showing endometritis, and ultrasound examination findings showing thickened fluid-filled tubes with or without free pelvic fluid or tuboovarian complex. **Because of the clinical similarity between PID and ectopic pregnancy, a serum pregnancy test should be performed on all patients suspected of having PID.**

Determination of appropriate treatment should consider pregnancy status, severity of illness, and compliance. **Less-severe disease can generally be treated on an outpatient basis. Women who are pregnant, have HIV, or have severe disease generally require inpatient therapy and treatment with parenteral antibiotics.** Table 22–1 lists PID treatment regimens.

Patients who have PID need to be aware of potential complications, including the potential for recurrence of disease, the development of tuboovarian abscess, chronic abdominal pain, infertility, and the increased risk of ectopic pregnancy. It is important to discuss these potential problems with patients who are given a diagnosis of PID. All patients with STDs or who are at risk for developing STDs should be counseled on safer sexual practices, including abstinence, monogamy, and the use of latex condoms.

Table 22–1 TREATMENT REGIMENS FOR PID

ORAL

Regimen A
- Ofloxacin 400 mg po bid for 14 d *or* Levofloxacin 500 mg po bid for 14 d
- *With or without* metronidazole 500 mg po bid for 14 d

Regimen B
- Ceftriaxone 250 mg IM single dose *or* Cefoxitin 2 g IM with probenecid 1 g po given concurrently
- *plus* Doxycycline 100 mg po bid for 14 d
- *With or without* Metronidazole 500 mg po bid for 14 d

PARENTERAL

Regimen A
- Cefotetan 2 g IV every 12 h *or* Cefoxitin 2 g IV every 6 h
- *plus* Doxycycline 100 mg po *or* IV every 12 h

Regimen B
- Clindamycin 900 mg IV every 8 h
- *plus* Gentamicin 2 mg/kg loading dose followed by 1.5 mg/kg IV of 8 h

Regimen C
- Ofloxacin 400 mg IV every 12 h *or* Levofloxacin 500 mg IV daily
- *With or without* Metronidazole 500 mg IV every 8 h

Regimen D
- Ampicillin/sulbactam 3 g IV every 6 h plus Doxycycline 100 mg po or IV of 2 h

Comprehension Questions

22.1 A 24-year-old nulliparous woman is noted to have a bothersome vaginal discharge. On examination, she is found to have a homogenous discharge with a fishy odor. Which of the following characteristics is likely to be noted on examination of the discharge?

A. Motile protozoa on wet mount
B. pH more than 4.5
C. Strawberry cervix on speculum examination
D. Budding hyphae on KOH examination

22.2 A 38-year-old woman complains of vaginal discharge and irritation. She notes having had a urinary tract infection 10 days previously, with resolution of her symptoms. Which of the following is the best therapy for her condition?

A. Oral metronidazole
B. Vaginal metronidazole
C. Oral fluconazole
D. Oral clindamycin
E. Oral estrogen and progestin therapy

22.3 A 24-year-old woman is noted to have lower abdominal tenderness, cervical motion tenderness, and a vaginal discharge. She has a low grade fever of 100.5°F (38.0°C). Which of the following is the best therapy for her condition?

A. Ceftriaxone intramuscularly and doxycycline orally
B. Ampicillin orally and azithromycin orally
C. Metronidazole orally as a single dose
D. Ciprofloxacin orally as a single dose

ANSWERS

22.1 **B.** This discharge of homogenous and fishy odor is most likely bacterial vaginosis associated with an alkaline pH. Partner treatment is not necessary for bacterial vaginosis. Oral metronidazole is one treatment.

22.2 **C.** This patient most likely has candida vulvovaginitis, since her discharge appeared after her cystitis, likely treated with antibiotics. A treatment for candida vulvovaginitis includes fluconazole or topical azole agents such as miconazole.

22.3 **A.** An option for outpatient therapy of salpingitis (PID) is IM ceftriaxone and oral doxycycline. Oral metronidazole as a single dose is a treatment for trichomonas vaginitis.

Clinical Pearls

- Remember to treat sexual partners when you diagnose a sexually transmitted infection and consider testing for infections that may initially be asymptomatic, such as HIV, hepatitis B and C, and syphilis.
- Single-dose therapy is available for many types of infections, including *Trichomonas,* gonococcal and chlamydial cervicitis, and candida vaginitis. Providing single-dose therapy in your office will improve your patient's compliance, as well as rates of successful treatment.

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Case 23

A 62-year-old man presents to your office for a routine evaluation. His only complaint is of fatigue over the past 2 to 3 months despite no changes in diet or lifestyle. On questioning, the patient reports that he has never smoked and admits to an increase in his consumption of alcohol upon retiring, to about two to three beers per day. He has occasional headaches on the day after a night of heavier drinking, which are easily relieved by the use of over-the-counter nonsteroidal anti-inflammatory drug (NSAID) preparations. While talking to the patient and examining his chart you note no distress and proceed with your examination. You note a 4 lb weight loss since his last visit 6 months ago and a relative increase in his pulse with a blood pressure of 129/81 mm Hg. Remarkable to this visit is the paleness of his conjunctivae, but the rest of his general examination is unchanged from the previous examination. You perform a digital rectal examination and find a smooth, normal-size prostate and some soft, reducible protrusions within the internal sphincter, along with guaiac-positive stools. You decide on a more direct approach and delve into his drinking, bowel habits, and NSAID use. His only addition is the occasional production of bloody stools accompanied by some diffuse abdominal discomfort.

- What is the most likely diagnosis?
- What is your next diagnostic step?
- What is the next step in therapy?

ANSWERS TO CASE 23:
Lower Gastrointestinal Bleeding

Summary: A 62-year-old man presents to your office for a routine checkup. He reports having occasional bloody stools and you discover guaiac-positive stools. He is a bit pale, but hemodynamically stable at the moment. You decide that further evaluation of this bleeding is necessary, but most of it can be carried out on an outpatient basis with close follow-up.

- **Most likely diagnosis:** Hemorrhoids.
- **Next diagnostic step:** Complete blood count (CBC) and colonoscopy.
- **Next step in therapy:** Discontinue NSAID use and decrease alcohol consumption.

ANALYSIS

Objectives

1. Know how to recognize the subtle signs and symptoms of lower GI bleeding.
2. Understand the etiologies of lower GI bleeding.
3. Understand how to correctly evaluate and treat patients with lower GI bleeding in outpatient settings.

Considerations

This 62-year-old man presented to your office for a routine examination but was found to have some type of lower gastrointestinal bleeding that needs further evaluation. During his office visit there are no signs of hemodynamic instability or active bleeding that require immediate referral to an emergency room or inpatient treatment, so you decide on close outpatient follow-up during his workup. His immediate identifiable and modifiable risk factors for GI bleeding include the regular consumption of alcohol and NSAIDs. You counsel him on both these matters and send him to the lab for a CBC, chemistry panel, liver function tests, and coagulation profile prior to his discharge home from your office. Barring any abnormal lab values that require emergent management, you schedule him for an outpatient colonoscopy later in the week. Your differential diagnosis at this time is wide but you start to consider the most frequent offenders in his age group, which include diverticular disease, hemorrhoids, tumors, and ulcerative colitis. For the time being, you modify those factors that may contribute to any of these etiologies and await the results of his laboratory tests.

APPROACH TO
Lower Gastrointestinal Bleeding

DEFINITIONS

HEMATOCHEZIA: Bright red blood visible in the stool.

LOWER GI BLEEDING: Bleeding that comes from a source distal to the ligament of Treitz.

CLINICAL APPROACH

The manifestations of GI bleeding depend on the source, rate of bleeding, and underlying or coexisting disease. An older patient, or someone with significant comorbidities, such as coronary artery disease, would be at a higher risk of presenting in shock. A younger, healthier individual may present with symptoms such as fatigue or dyspnea on exertion, or may complain directly of seeing blood in the stool. Signs and symptoms of anemia are common and include weakness, easy fatigability, pallor of the conjunctivae or skin, chest pain, dizziness, tachycardia, hypotension, and orthostasis.

A history of blood in the stool or finding guaiac-positive stool on examination should prompt further evaluation to determine the source of the bleeding. Depending on a patient's history and hemodynamic status, more immediate and invasive measures may be necessary once GI bleeding is identified. For example, **hematochezia is usually pathognomonic of lower GI bleeding, but can also be found in patients with heavy upper GI bleeding.** In this setting, a nasogastric aspirate may help differentiate this small subset of patients.

Evaluation of the "ABCs" (airway, breathing, and circulation) is critical in unstable patients who present with GI bleeding. ICU admission should not be delayed in those with severe bleeding and a team approach, consisting of a gastroenterologist, a surgeon with expertise in GI surgery, and skilled nursing, should always be anticipated. Major causes of morbidity and mortality in patients with GI bleeding include blood aspiration and shock. To prevent these complications, endotracheal intubation should always be considered to protect the airway of patients with altered mental status. Most lower GI bleeding does not warrant emergency therapy, but be prepared for decompensation in the elderly and in those with borderline normal hemodynamic parameters.

Diagnosis

The test of choice for the determination of the source of lower GI bleeding is colonoscopy. Adequate bowel preparation with an oral sulfate purge to clear the bowel of blood, clots, and stool increases the yield in diagnosing colonic bleeding sites. Angiography and technetium-labeled colloid or red

blood cell scans may be of value if colonoscopy cannot be performed or if heavy bleeding prevents adequate visualization of the colon. However, the magnitude of bleeding required to show the bleeding site limits their usefulness. Sigmoidoscopy with air-contrast barium enema x-rays may be an alternative when colonoscopy is unavailable or if the patient refuses colonoscopy. If the initial sigmoidoscopy is negative, a colonoscopy must be performed. If both of these studies are negative, panendoscopy should be carried out.

Always consider the possibility of upper GI bleeding as a source of hematochezia. An aspirate from a nasogastric tube can help to make this determination. An aspirate that shows bile but not blood will help to confirm that the bleeding is from a lower GI source.

ETIOLOGIES

Hemorrhoids

Hemorrhoids are dilated veins in the hemorrhoidal plexus of the anus. They are defined as "internal" if they arise above the dentate line and "external" if they arise below the dentate line; both can be the cause of hematochezia. Chronic constipation, straining for bowel movements, pregnancy, and prolonged sitting (eg, truck drivers) are risk factors. Along with bleeding, external hemorrhoids can cause pain, irritation, and a palpable lump. Internal hemorrhoids can cause bleeding and can prolapse through the anus. Conservative treatment with a high-fiber diet, stool softeners, and precautions against prolonged straining are usually successful. When necessary, various surgical procedures can be performed for definitive treatment.

Diverticular Disease

Diverticula are outpouchings of the colonic mucosa through weakened areas of the colon wall. They occur most often where blood vessels penetrate through the muscles of the colon. They are **most often asymptomatic and found on endoscopy or bowel imaging studies.** They can cause symptomatic, and occasionally massive, bleeding that is usually painless. Diverticular bleeding usually stops spontaneously. When the bleeding is extremely heavy or fails to stop, surgical resection of the affected portion of the colon may be necessary. Asymptomatic diverticulosis is managed with dietary modification, primarily a high-fiber diet.

Diverticulitis is a painful inflammation and infection of a diverticulum. Diverticulitis frequently causes left lower quadrant abdominal pain along with fever, nausea, diarrhea, and constipation. Perforation of a diverticulum resulting in peritonitis or intraabdominal abscess formation can be a complication. Diverticulitis is typically treated with bowel rest and antibiotics effective against gut flora. A combination of a quinolone and an agent for anaerobic

organisms, such as metronidazole, is one commonly used regimen. In severe cases, recurrent cases, or when perforation occurs, surgery may be indicated.

Inflammatory Bowel Disease

Ulcerative colitis and Crohn disease are the two primary diagnoses considered in the category of inflammatory bowel disease (IBD). **Ulcerative colitis causes continuous inflammation of the large bowel,** starting from the rectum and extending proximally. Severe disease can cause pancolitis, affecting the entire colon. **Crohn disease causes areas of focal inflammation, but can occur anywhere in the gastrointestinal tract.** Both diseases can cause recurrent episodes of abdominal pain, diarrhea, weight loss, rectal bleeding, fistulas, and abscesses. The definitive etiology of IBD is not known, but these are autoimmune syndromes and a family history of IBD is a major risk factor. Along with GI symptoms**, numerous extraintestinal manifestations may occur, most frequently arthritis.** Other extraintestinal manifestations include sclerosing cholangitis, cirrhosis, fatty liver, pyoderma gangrenosum, and erythema nodosum. Ulcerative colitis is a significant risk factor for the development of colon cancer. Patients with ulcerative colitis require frequent surveillance colonoscopic examinations. IBD can be managed with symptomatic therapy, such as antidiarrheal medications, along with anti-inflammatory medications (aminosalicylates, corticosteroids) given orally or as enemas, and immunosuppressive medications. Ulcerative colitis can be definitively treated with a total colectomy, which is usually reserved for severe pancolitis, failure to respond to medical therapy, or because of the risk of colon cancer.

Colon Neoplasms

Polyps are benign neoplasms of the colon. Hyperplastic polyps tend to be small, smooth growths found incidentally during endoscopy and are of no prognostic significance. Adenomatous polyps are benign growths that have a potential to become malignant. Listed in order of potential for becoming cancerous (from least to most), the three types of adenomas are tubular adenomas, tubulovillous adenomas, and villous adenomas. Larger polyps have a higher risk of causing bleeding and becoming malignant than smaller polyps. Polyps can be identified and removed during a colonoscopy.

Colon cancer is the second leading cause of cancer deaths in men and women. The risk of colon cancer increases with age, with a history of colon polyps, a family history of colon cancer, or a personal history of ulcerative colitis. **Any patient older than age 50 years who has lower GI bleeding must be evaluated for the presence of colon cancer.** Because of the presence of premalignant lesions (polyps) that can be identified and removed in asymptomatic patients, colon cancer screening is recommended for all adults older than age 50, and at younger ages for those with increased risks. The treatment and prognosis of colon cancer depends upon the stage in which it is found.

The Dukes System stages colon cancer from A to D, depending on the penetration through the bowel wall layer, the presence of lymph node spread, and distant metastases. Dukes A colon cancer has an excellent prognosis with surgical resection; Dukes D cancer is usually not curable and is treated with combinations of surgery, chemotherapy, and radiation.

Diverticular bleeding occurs in 10% to 20% of cases of lower GI bleeding, with most cases being increased by NSAID or aspirin use. In diverticular disease, bleeding is often self-limited and ceases approximately 75% of the time, while recurring at a rate of approximately 38%. More common causes include hemorrhoids (59%), colorectal polyps (38%-52%), diverticulosis (34%-51%), colorectal cancer (8%), ulcerative colitis, arteriovenous malformations, and colonic strictures. These percentages vary amongst age groups and most serious causes are expected in the elderly.

Comprehension Questions

23.1 A 52-year-old man presents with bright red blood per rectum. He states that he has been bleeding heavily for a couple of hours. In the emergency room (ER), his pulse is 110 beats/min, blood pressure is 90/50 mm Hg, he is cool and clammy appearing, and he has blood present on rectal examination, although he does not appear to be bleeding at the present. Which of the following is the best initial next step?

A. Colonoscopy.
B. Flexible sigmoidoscopy.
C. Place a nasogastric tube.
D. Start a bolus of IV normal saline.
E. Give a transfusion of type O-negative blood.

23.2 On a screening colonoscopy a patient is noted to have several diverticuli in the sigmoid colon. He has never had any complaints of constipation, diarrhea, abdominal pain, or rectal bleeding. Which of the following is the best step in the management of this patient?

A. Annual colonoscopy
B. Sigmoid colectomy
C. High fiber diet
D. Proton pump inhibitor

23.3 A 25-year-old man has a colonoscopy for diagnostic evaluation of abdominal pain, weight loss, diarrhea, and blood in the stool. The colonoscopy shows diffuse mucosal inflammation from the anus to the terminal ileum. Which of the following is the most likely diagnosis?

A. Ulcerative colitis
B. Crohn disease
C. Pseudomembranous colitis
D. Colon cancer

ANSWERS

23.1 **D.** The initial evaluation of this acutely ill patient is "ABC"—airway, breathing, and circulation. As he appears to be in hypovolemic shock, with tachycardia and hypotension, a bolus of a crystalloid fluid, such as normal saline or lactated Ringer's solution, is necessary before proceeding with any of the other evaluations.

23.2 **C.** Asymptomatic diverticuli are a common finding on screening colonoscopies. The initial management of this is a high-fiber diet. Diverticulosis by itself does not increase one's risk of developing colon cancer. Surgery is typically reserved for severe or recurrent symptomatic cases.

23.3 **A.** Ulcerative colitis causes continuous inflammation of the colon, whereas Crohn disease causes patchy inflammation with skip areas. Pseudomembranous colitis is a complication of *Clostridium difficile* infection of the colon.

Clinical Pearls

- Lower GI bleeding is usually suspected in lesions or pathology that is distal to the angle of Treitz. Simple measures like nasogastric lavage can aid in ruling out upper GI bleeding as a cause of hematochezia.
- In a patient with acute lower GI bleeding, consider performing colonoscopy. Other diagnostic procedures that may be useful include radionuclide imaging and mesenteric angiography.
- Any patient older than age 50 years should be screened for colon cancer.

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Case 24

A 61-year-old woman presents to the emergency room complaining of cough for 2 weeks. The cough is productive of green sputum and is associated with sweating, shaking chills, and fever up to 102°F (38.8°C). She was exposed to her grandchildren who were told that they had upper respiratory infections 2 weeks ago but now are fine. Her past medical history is significant for diabetes for 10 years, which is under good control using oral hypoglycemics. She denies tobacco, alcohol, or drug use. On examination, she looks ill and in distress, with continuous coughing and chills. Her blood pressure is 100/80 mm Hg, her pulse is 110 beats/min, her temperature is 101°F (38.3°C), her respirations are 24 breaths/min, and her oxygen saturation is 97% on room air. Examination of the head and neck is unremarkable. Her lungs have rhonchi and decreased breath sounds, with dullness to percussion in bilateral bases. Her heart is tachycardic but regular. Her extremities are without signs of cyanosis or edema. The remainder of her examination is normal. A complete blood count (CBC) shows a high white blood cell (WBC) count of 17,000 cells/mm^3, with a differential of 85% neutrophils and 20% lymphocytes. Her blood sugar is 120 mg/dL.

- What is the most likely diagnosis?
- What is your next diagnostic step?
- What is the next step in therapy?
- What are potential complications of this diagnosis?

ANSWERS TO CASE 24:
Pneumonia

Summary: This is a 61-year-old woman with fever, chills, and productive cough. She has an abnormal pulmonary examination and is found to have a high white cell count. Her significant medical history is diabetes mellitus.

- **Most likely diagnosis:** Community-acquired pneumonia.
- **Next diagnostic step:** Chest x-ray, sputum Gram stain and culture, and blood cultures.
- **Next therapeutic step:** Determine whether the patient requires in-patient or out-patient therapy and start antibiotics.
- **Potential complications:** Bacteremia, sepsis, parapneumonic pleural effusion, and empyema.

ANALYSIS

Objectives

1. Recognize the differential diagnosis of pneumonia.
2. Be familiar with widely accepted decision-making strategies for the diagnosis and management of different kinds of pneumonia.
3. Learn about the treatment and follow-up of pneumonia.
4. Recognize the effects of comorbid conditions.

Considerations

This 61-year-old patient presents with a common diagnostic dilemma: productive cough with green sputum and fever. The first priority for the physician is to assess whether the patient is more ill than the complaint would indicate. Helpful clues to the patient's overall condition include a toxic appearance, using accessory muscles to breathe, and low oxygen saturation. Tachycardia, hypotension, and altered mentation are signs of more critical illness. **Airway, breathing, and circulation must always be addressed.**

Fortunately, this patient does not have those alarming symptoms. If a patient has respiratory distress, the physician may need to check arterial blood gases. If the patient has low oxygen saturation, give oxygen by nasal cannula and then proceed to your history and physical examination.

The most common etiology of cough is an upper respiratory tract infection. This patient has several features that make pneumonia more likely, including

her **age, cough with green sputum, fever with chills, and exposure to close contacts with respiratory infections.** The gold standard for diagnosis of pneumonia is the presence of an infiltrate on chest x-ray, although normal x-ray does not exclude the diagnosis. X-rays may be normal early in the course of disease and a patient who is dehydrated may not demonstrate an infiltrate until the patient is adequately rehydrated.

APPROACH TO
Pneumonia

DEFINITIONS

PNEUMONIA: Infection of lung parenchyma caused by agents that include bacteria, viruses, fungi, and parasites.

PNEUMONITIS: An inflammation of the lungs from a variety of noninfectious causes such as chemicals, blood, radiation, and autoimmune processes.

CLINICAL APPROACH

Bronchitis and pneumonia represent a continuum of lower respiratory infection. The extent of involvement of adjacent lung parenchyma determines whether there is an infiltrate on x-ray. **Pneumonia is defined as infection of lung parenchyma** caused by agents that include bacteria, viruses, fungi, and parasites. It should be distinguished from pneumonitis, which is an inflammation of the lungs from a variety of noninfectious causes such as chemicals, blood, radiation, and autoimmune processes. The occurrence and severity of pneumonia depends on both the state of the body's defense mechanism against infection and the characteristics of the infectious agent. The **most common mechanism triggering pneumonia is upper airway colonization** by potentially pathogenic organisms that are subsequently aspirated. The type of organism involved depends, in part, on host characteristics.

Community-Acquired Pneumonia

Pneumonia that occurs in persons who are not hospital in-patients or residents of long-term care facilities is defined as community acquired. The most common bacterial cause of community-acquired pneumonia is *Streptococcus pneumoniae* (pneumonococcus). Other common bacterial etiologies are *Haemophilus influenzae* and *Moraxella catarrhalis*. Pneumococcal pneumonia classically causes an illness of acute onset with cough productive of rust-colored sputum, fever,

shaking chills, and a lobar infiltrate on chest x-ray. *H influenzae* is often seen in patients with underlying chronic obstructive pulmonary disease.

Mycoplasma pneumoniae, *Chlamydia pneumoniae*, and *Legionella pneumophila* are bacteria that cause what is classified as "atypical" pneumonia. Atypical pneumonia is also caused by several different viruses. The **typical pneumonia organisms are more common in the very young and in the older patient.** Atypical pneumonias occur more commonly in adolescent or young adult patients. Atypical organisms tend to cause bilateral, diffuse infiltrates, rather than focal, lobar infiltrates, on x-ray.

Hospital-Acquired Pneumonia

Hospital-acquired pneumonia is a major source of morbidity, mortality, and prolonged hospitalization. **Risk factors include intubation, nasogastric tube feeding, preexisting lung disease, and multisystem failure.** The organisms involved include the pathogens involved in community-acquired pneumonia as well as aerobic gram-negative bacteria (*Pseudomonas*, *Klebsiella*, *Acinetobacter*) and gram-positive cocci such as *Staphylococcus aureus*. The incidence of drug-resistant organisms, such as methicillin-resistant *S aureus*, is increasing. Avoiding intubation when possible, using oropharyngeal intubation as opposed to nasopharyngeal intubation, keeping the head of the patient's bed elevated during tube feedings, and infection control techniques, such as careful hand washing and use of alcohol-based hand disinfectants, can reduce risks.

Diagnosis

Patient history in pneumonia commonly includes the symptoms of productive cough, fever, pleuritic chest pain, and dyspnea. The symptoms can be very nonspecific in the very old and very young. In young children, rapid breathing is commonly seen; in the elderly, pneumonia may present as altered mental status.

Sometimes the history may lead to assistance in determining the specific organism involved. An abrupt onset or abruptly worsening illness is seen frequently in pneumococcal pneumonia. *Legionella* often causes diarrhea along with pneumonia. *S aureus* is a common cause of postinfluenza pneumonia.

Physical examination findings can include fever, tachycardia, tachypnea, hypotension, and reduced oxygen saturation. Auscultation of the lungs may reveal rhonchi or rales. Egophony (E to A change) can be a sign of focal lung consolidation and dullness to percussion may be the result of a pulmonary effusion.

All patients with suspected pneumonia should have a chest x-ray. The presence of an infiltrate can confirm the diagnosis. Absence of an infiltrate does not rule out pneumonia as a diagnosis. A chest x-ray can also identify a pleural effusion, which may be a complication of pneumonia (parapneumonic effusion).

Specific x-ray findings may also lead to consideration of certain etiologic agents or types of pneumonia. As noted previously, lobar infiltrates are more common with typical infections and diffuse infiltrates are more likely with atypical infections. A bilateral, "ground glass"-appearing infiltrate is associated with *Pneumocystis jiroveci* (formerly known as *P carinii)* infections, which are seen most often in patients with AIDS. Apical consolidation may be seen with tuberculosis. Pneumonia caused by the aspiration of gastrointestinal contents commonly is seen in the right lower lobe because of the branching of the bronchial tree.

Other testing indicated in patients with pneumonia includes a complete blood count (CBC) and a chemistry panel. Specific microbiologic diagnosis is possible with blood or sputum cultures. **Cultures have a low sensitivity** (many false negatives), but a positive culture can help to guide treatment. Direct fluorescent antibody testing on sputum can be used to identify *Legionella* and *Mycoplasma; Legionella* can also be identified by urinary antigen testing.

Treatment

When pneumonia is diagnosed, the initial decision to be made is can the patient be treated safely as an outpatient or is hospitalization required. One method of making this determination is to use the **Pneumonia Severity Index, which assigns patients to a risk category based on their age, comorbid illnesses, specific examination, and laboratory findings.** High-risk comorbidities include neoplastic disease, liver disease, renal disease, congestive heart failure, and diabetes. Physical examination findings taken into consideration are tachypnea, fever, hypotension, tachycardia, and altered mental status. Laboratory findings include a low pH, low serum sodium, low hematocrit, low oxygen saturation, high glucose, high blood urea nitrogen (BUN), and pleural effusion on x-ray. Based on the patient's demographics and individual findings, a risk class and mortality risk is assigned. Low-risk classes (classes 1 and 2) can be safely treated as an outpatient; higher-risk classes (classes 3, 4, and 5) should be hospitalized.

The emergence of drug-resistant pneumococci and the development of new antimicrobials have changed the empiric treatment of community-acquired pneumonia. In healthy persons, a macrolide (clarithromycin or azithromycin) or doxycycline is recommended empiric therapy. In areas with high rates of macrolide resistance, treatment with a newer fluoroquinolone (levofloxacin, moxifloxacin) or the combination of a β-lactam plus a macrolide would be recommended.

For hospitalized patients with community-acquired pneumonia who do not require ICU treatment, an intravenous β-lactam (eg, cefuroxime, cefotaxime, ceftriaxone, or ampicillin-sulbactam) and an intravenous macrolide (erythromycin or azithromycin) are recommended. An IV fluoroquinolone with activity against *S pneumoniae* can be substituted.

The follow-up visit to the office 3 to 4 days later will help to assess response to therapy. Early follow-up chest x-rays are mandatory in those who fail to

show clinical improvement by 5 to 7 days, because bronchogenic carcinoma can present with the picture of a typical pneumonitis.

Hospital-acquired pneumonias require broader antibiotic coverage of the likely pathogens, many of which have developed multiple-drug resistance. One regimen includes a β-lactam plus an antipseudomonal fluoroquinolone or aminoglycoside. Methicillin-resistant *S aureus* may require treatment with vancomycin.

The duration of the treatment is influenced by the severity of illness, the etiologic agent, response to therapy, the presence of other medical problems, and complications. Therapy until the patient is afebrile for at least 72 hours is usually sufficient for pneumonia caused by *S pneumoniae*. A minimum of 2 weeks of therapy is appropriate for pneumonia caused by *S aureus*, *Pseudomonas aeruginosa*, *Klebsiella*, anaerobes, M *pneumoniae*, C *pneumoniae*, or *Legionella* species.

Complications

Bacteremia occurs in approximately 25% to 30% of patients with pneumococcal pneumonia. Mortality rates range for patients with bacteremia from 20% to 30%, but can be as high as 60% in the elderly. Parapneumonic pleural effusion develops in 40% of hospitalized patients with pneumococcal pneumonia. Fewer than 5% of cases progress to empyema. If more than a minimal amount of fluid is present, as evidenced by significant blunting of the costophrenic angle on x-ray, it may be necessary to perform a thoracentesis with Gram stain and culture of the pleural fluid. The presence of an empyema usually requires drainage with a chest tube or surgical procedure.

Prevention

Pneumococcal vaccine is recommended for all persons aged 65 years and older, all adults with chronic cardiopulmonary diseases, and all immunocompromised persons. Consider revaccination every 5 years in patients known to have a rapid decline in antibody titers, such as those with nephritic syndrome or renal failure. Also consider repeating pneumococcal vaccination in asplenic patients. Revaccination has minimal side effects; the most common is a localized reaction at the site of injection.

Influenza vaccination is recommended in the late fall and winter months for populations at risk for infection, complications, or transmission of the influenza virus. The association between influenza virus infection and pneumonia is well recognized. The number of cases of invasive pneumococcal disease peaks in midwinter, when influenza is prevalent. Influenza virus infection can facilitate bacterial colonization and impair host defense mechanism. A prospective study of patients 65 years of age and older demonstrated the effectiveness of influenza and pneumococcal vaccination at reducing hospitalizations for pneumonia and at preventing invasive pneumococcal disease.

Comprehension Questions

24.1 A 17-year-old adolescent male presents to the ER with a temperature of 101.0°F (38.3°C), a deep nonproductive cough, and generalized malaise for 3 days. He doesn't recall being around any particular sick contacts but is around many people in his after-school job in sales and at school. He states that he never had the chicken pox and is unaware of what immunizations he received as a child. He was diagnosed at age 12 with leukemia but has since been healthy. He is worried that his cancer may no longer be in remission. A chest x-ray reveals bilateral, diffuse infiltrates on chest x-ray. Which of the following is the most likely cause of illness?

A. Pneumonia caused by *S pneumonia*
B. Pneumonia caused by *P jiroveci*
C. Pneumonia caused by Legionella pneumophila
D. Pneumonia caused by M *pneumonia*
E. *Pneumonia caused by H influenza*

24.2 A 35-year-old woman patient returns to clinic with a temperature of 104.0°F, night sweats, chills, shortness of breath, and cough productive of yellowish-green sputum. She was seen 2 weeks ago for headache, fever of 102.0°F, nonproductive cough, and myalgias. She was prescribed a dose of oseltamavir for 10 days. She felt better after taking the medication but now feels she is getting worse. Which of the following is the best treatment for this patient?

A. 14-day trial of oseltamavir
B. Erythromycin
C. Penicillin
D. Cefuroxine
E. No treatment needed

24.3 A 76-year-old widowed man who lives alone presents to clinic with increasing shortness of breath and chest pain at rest for the past 2 weeks. He has had chronic hypertension and CAD for 20 years for which he takes HCTZ, enalapril, and aspirin 81 mg daily. Other medical problems include hyperlipidemia, peripheral vascular disease, and gastroesophageal reflux disease (GERD) which are controlled by lovastatin, warfarin, and omeprazole. Two years ago he suffered a cerebrovascular accident that was localized to the brainstem. He now has dysphagia and is noted to cough frequently at night. He has no cough at present and has not been able to take his temperature at home. Which of the following is the best next step?

A. Upper endoscopy
B. Removal of ACE inhibitor
C. Nitroglycerine patch
D. Chest radiograph

ANSWERS

24.1 **D.** Bilateral, diffuse infiltrates are more likely to be seen in patients with pneumonia caused by atypical agents, such as *Mycoplasma*, than in patients with typical pneumonia or aspiration pneumonia. Legionella, another atypical pneumonia, is unlikely in this patient population and the patient did not have diarrhea. It is more likely that the patient contracted an atypical pneumonia than having a relapse of leukemia with such profound immunodeficiency with no prior symptoms.

24.2 **B.** This patient is suffering from bacterial pneumonia caused by *S Aureus* which is a common infection seen after influenza infection. Oseltamavir is not needed because the cause of her illness is no longer viral. A 10-day trial is what is often prescribed to patients. *Streptococcus pneumonia* would be treated with penicillin. Pneumonia caused by bacterial hemophilus influenza would be treated with Cefuroxime. Erythromycin is the drug of choice for pneumonias caused by *Legionella* or *S Aureus*.

24.3 **D.** This patient most likely has aspiration pneumonia. With impairment of the gag reflex after cerebrovascular accident (CVA), he is more likely to aspirate during sleep, indicated by his cough. His GERD is well controlled by medication so upper endoscopy is not warranted at this time. Nitroglycerine patches may be indicated if he described symptoms more related to angina. An ACE inhibitor would cause a cough unrelated to time of day.

Clinical Pearls

- Elderly patients often have fewer or less-severe symptoms or atypical presentations of pneumonia. Consider pneumonia in the differential diagnosis of altered mental status in the elderly.
- Appropriate use of influenza and pneumococcal vaccination reduces the risk of pneumonia in susceptible populations.
- Consider the diagnosis of empyema in patients with pneumonia and a pleural effusion, especially if the patients continue to have fever despite appropriate antibiotic therapy.

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Case 25

A 38-year-old woman presents to the office with complaints of weight loss, fatigue, and insomnia of 3-month duration. She reports that she has been feeling gradually more tired and staying up late at night because she can't sleep. She does not feel that she is doing as well in her occupation as a secretary and states that she has trouble remembering things. She does not go outdoors as much as she used to and cannot recall the last time she went out with friends or enjoyed a social gathering. She feels tired most of the week and states she feels that she wants to go to sleep and frequently does not want to get out of bed. She denies any recent medication, illicit drug, or alcohol use. She feels intense guilt regarding past failed relationships because she perceives them as faults. She states she has never thought of suicide, but has begun to feel increasingly worthless.

Her vital signs and general physical examination are normal, although she becomes tearful while talking. Her mental status examination is significant for depressed mood, psychomotor retardation, and difficulty attending to questions. Laboratory studies reveal a normal metabolic panel, normal complete blood count, and normal thyroid functions.

- What is the most likely diagnosis?
- What is your next step?
- What are important considerations and potential complications of management?

ANSWERS TO CASE 25:
Major Depression

Summary: This is a 38-year-old woman with depression. She meets at least five of the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (DSM-IV) diagnostic criteria during a 2-week period that represents a change from her previous level of functioning. At least one of the symptoms must be either depressed mood or loss of interest or pleasure.

- **Most likely diagnosis:** Major depression.
- **Next step:** Evaluate the patient for suicidal risk, begin pharmacologic and psychotherapeutic management.
- **Important considerations and potential complications:** Rule out other medical diagnoses such as hypothyroidism, anemia, and infectious processes that could mimic some symptoms of depression; verify that no substance abuse or use is taking place; screen for bipolar disorder and inquire about a family history of mood disorders; investigate and address suicidal ideations; review any recent medication changes for agents that may contribute to these symptoms (eg, β-blockers, steroids, sedatives, chemotherapy agents).

ANALYSIS

Objectives

1. Recognize the common presenting signs and symptoms of depression.
2. Understand the multifactorial pathogenesis of depression.
3. Learn about the treatment of depression and the sequelae of this condition.
4. Be familiar with the appropriate follow-up of this condition.
5. Recognize the importance of assessing for suicidal risk.

APPROACH TO
Depression

DEFINITIONS

MAJOR DEPRESSION: One or more episodes of mood disorder each of which lasts at least 2 weeks. The most prominent symptoms of major depressive disorder are depressed mood and loss of interest or pleasure. Insomnia and weight loss often accompany major depression, but depressed patients may also have weight gain and hypersomnia.

DYSTHYMIC DISORDER: A chronic depression of mood which does not meet the criteria for major depression, in terms of either severity or duration of individual episodes, yet the patient still has loss of interest, lack of appetite or pleasure, and low energy.

CLINICAL APPROACH

Background

Depression has a lifetime prevalence of 15% to 25%, with a **greater incidence in women and the elderly.** Symptoms for depression must include at least 5 of the 9 following symptoms, must occur during the same 2-week time period, must represent a change from previous functioning, and must include either depressed mood or loss of interest or pleasure:

1. Depressed mood
2. Diminished interest or pleasure
3. Significant weight loss or weight gain
4. Insomnia or hypersomnia
5. Psychomotor agitation or retardation
6. Fatigue or loss of energy
7. Feelings of worthlessness
8. Diminished ability to think or concentrate; indecisiveness
9. Recurrent thoughts of death, suicidal ideation, suicide attempt, or specific plan

Also,

- Symptoms do not meet criteria for a mixed episode (both mania and depressive episode).
- Symptoms cause clinically significant distress or impairment of functioning.
- Symptoms are not a result of the direct physiologic effects of a substance or a generalized medical condition.
- Symptoms are not accounted for by bereavement.

A patient with depression commonly presents to the physician with various somatic complaints and decreased energy level rather than a complaint of depression. Patients often complain of sadness, sometimes of irritability or mood swings. Difficulty concentrating or loss of energy and motivation are common. Their thinking is often negative, frequently with feelings of worthlessness, hopelessness, or helplessness. Poor memory or concentration may be a complaint in others. The elderly may present with confusion or a general decline in functioning. **The diagnosis of depression needs to be considered in scenarios where a patient presents with multiple unrelated physical symptoms.**

The differential diagnosis of depression includes many other psychiatric and medical disorders. The psychiatric disorders include dysthymic disorder,

bereavement, and bipolar disorder. **Numerous medical conditions can cause depressive symptoms.** Common among these are hypothyroidism and anemia. The role of pharmacologic agents and substance use, abuse, or dependence also should be investigated, as these can cause significant mood changes. This is especially true of alcohol, sedatives, narcotics, and cocaine.

Pathophysiology

The etiology of depression is thought to be multifactorial, involving a complex interaction of genetic, psychosocial, and neurobiologic factors. Multiple neurotransmitter systems are implicated, including the serotoninergic, noradrenergic, and dopaminergic systems. Evidence of the effects of neurotransmitters on mood disorders is supported by the knowledge of the mechanism of action of antidepressant medications. All currently available antidepressant agents appear to work by increasing the amount of neurotransmitter available to the postsynaptic nerve. They accomplish this by (1) enhancing neurotransmitter release, (2) reducing neurotransmitter breakdown, or (3) inhibiting the reuptake of the neurotransmitter by the presynaptic neuron.

Morbidity and Mortality

Depression causes significant morbidity and mortality in numerous ways. Depression is frequently reported in persons with underlying medical conditions. It is a common occurrence following myocardial infarctions and cerebrovascular accidents. Persons with depression and preexisting cardiovascular disease have a three and half times greater risk of dying of a heart attack than do nondepressed patients. Studies also show that **persons with depression have a greater chance of developing or dying from cardiovascular disease,** even after controlling for traditional risk factors such as smoking, blood pressure, and lipid levels. Depression also contributes the disruption of interpersonal relationships, the development of substance abuse, and absenteeism from work and school.

All depressed patients should be screened for suicidal and homicidal/violent ideations. A history of suicide attempts or violence is a significant risk factor for future attempts. Major depression plays a role in more than half of all suicide attempts. **Women, especially those younger than age 30 years, attempt suicide more frequently than men, but men are more likely to complete suicide**. Firearms are the most commonly used method in completed suicides. Table 25–1 lists the risk factors for suicide attempts and completed suicides.

Physical Findings

Most patients with depression have no significant physical abnormalities on examination. Those who have more severe symptoms may reveal decline in grooming or hygiene along with significant weight changes. Speech may be

Table 25–1 RISK FACTORS FOR SUICIDE ATTEMPTS AND COMPLETED SUICIDES

ATTEMPT	COMPLETED
Female sex	Male sex
Age <30 y	Age >55 y
Living alone	Concurrent chronic medical illness
Current psychosocial stressors (loss of job, relationship, etc)	Social isolation (divorced, widowed)
	History of suicide attempt
Substance abuse	Family history of suicide
Personality disorder	Substance abuse
Depression	Depression and family history of depression

Data from: American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. *4th ed. Washington, DC: American Psychiatric Association Press; 1994; and Guck TP, Kavan MG, Elsasser GN, Barone EJ. Assessment and Treatment of Depression following Myocardial Infarction.* Am Fam Physician. *2001;64:641-648,651-652.*

normal, slow, monotonic, or lacking in content. Pressured speech is suggestive of mania, whereas disorganized speech suggests the need to evaluate for psychosis. The thought content of patients with depression includes feelings of inadequacy, helplessness, or hopelessness. Sometimes patients complain of being overwhelmed. Psychomotor retardation can manifest as slowing of movements or reactions, especially in the elderly.

TREATMENT

Initial pharmacotherapy should be based on physician familiarity with medication, anticipated safety and tolerability, anticipation of adverse effects, and history of prior treatments. **Pharmacotherapy with psychotherapy is more effective than either pharmacotherapy or psychotherapy alone.** Treatment should be geared toward doing both to improve chances of successful therapy. Treatment failures typically result from medication noncompliance, inadequate duration of therapy, or inadequate dosing. No class of medication has been proven to be more effective than other classes. Patients treated for a first episode of major depression should be treated for at least 6 to 9 months; recurrent depression needs to be treated for longer periods of time. The need for lifelong therapy is higher with increasing number of episodes of depression. **All antidepressants carry an FDA "Black Box" warning that they increase the risk of suicidal thoughts and behaviors in children, adolescents, and young adults, especially in the first months of treatment**.

CLASSES OF MEDICATIONS

Table 25–2 lists the medications used in the treatment of depression.

Selective Serotonin Reuptake Inhibitors

Selective serotonin reuptake inhibitors (SSRIs) increase the amount of the neurotransmitter serotonin (5-hydroxytryptamine) available to the postsynaptic neuron by blocking the presynaptic neuron's ability to reuptake serotonin. Because it can take 3 to 6 weeks of therapy before significant improvement in mood occurs, dosage adjustments of these medications should occur no more often than monthly. These agents have a low risk of toxicity if taken as an overdose (either accidentally or intentionally), making them very safe to use. Common side effects include sexual dysfunction, weight gain, gastrointestinal disturbance, fatigue, and agitation. Because of their efficacy and safety, SSRIs are frequently used as first-line agents for the treatment of depression.

Serotonin-Norepinephrine Reuptake Inhibitors

Serotonin-norepinephrine reuptake inhibitors (SNRIs) affect both the serotonergic and noradrenergic systems. They act primarily on the serotonergic system at lower dosages and on the noradrenergic system at higher dosages. Their side effects are similar to SSRIs. They can be used as first-line treatment for depression and, because of their effects on two neurotransmitter systems, may be used as second-line agents in SSRI failure.

Table 25–2 MEDICATIONS USED IN THE TREATMENT OF DEPRESSION

SSRI	SNRI	TCA	ATYPICAL	MAOI
Fluoxetine (Prozac) Paroxetine (Paxil) Sertraline (Zoloft) Fluvoxamine (Luvox) Citalopram (Celexa) Escitalopram (Lexapro)	Venlafaxine (Effexor) Duloxetine (Cymbalta) Mirtazapine (Remeron)	Amitriptyline (Elavil) Nortriptyline (Pamelor) Desipramine (Norpramin) Clomipramine (Anafranil) Doxepin (Sinequan) Imipramine (Tofranil)	Bupropion (Wellbutrin) Amoxipine (Asendin) Trazodone (Desyrel)	Phenelzine (Nardil) Tranylcypromine (Parnate)

Tricyclic Antidepressants

Tricyclic antidepressants (TCAs) are older agents that affect, to varying degrees, the reuptake of norepinephrine and serotonin. They are effective for the treatment of depression and, because they have been in use for many years, are inexpensive. However, they have numerous side effects, including sedation, dry mouth, dry eyes, urinary retention, weight gain, and sexual disturbance. They also carry the risk that they are highly toxic and potentially fatal in overdose. Because of the side effects and risks, TCAs have largely been replaced by SSRIs as the first-line treatment of depression.

Monamine Oxidase Inhibitors

Monoamine oxidase inhibitors (MAOIs) cause increased amounts of serotonin and norepinephrine to be released during nerve stimulation. Patients taking MAOIs must be on a tyramine-restricted diet to reduce the risk of severe, and sometimes fatal, hypertensive crisis. MAOIs also interact with numerous other medications, including SSRIs and meperidine (Demerol). These interactions can also be fatal. Because of the risks, MAOIs should only be used by experienced practitioners and only when the benefits outweigh the risks.

Atypical Agents

The different atypical agents may act similarly to SSRIs, TCAs, and MAOIs, in varying degrees. Their primary benefit is a lower incidence of sexual disturbance as a side effect. Bupropion is associated with a risk of seizure at higher doses and is contraindicated in patients with a history of seizure disorders. Trazodone carries the risk, although rare, of causing priapism. It is also highly sedating and is frequently used as a sleep aid.

INPATIENT MANAGEMENT

Inpatient management is indicated when the patient presents a significant risk to self (suicide, inability to care for self) or others (risk of violence), or the symptoms are sufficiently severe to initiate treatment in controlled settings. Involvement of a psychiatrist is warranted in the care of patients in whom more severe symptoms require more intensive care (suicidal ideations, psychosis, mania, and severe decline in physical health).

OTHER MOOD DISORDERS

Anxiety Disorders

Anxiety disorders is a classification of mood disorders that are common in the population such as **panic disorder, obsessive-compulsive disorder** (OCD), **generalized anxiety disorder, posttraumatic stress disorder** (PTSD), **and**

phobia. Patients with generalized anxiety disorder have excessive and difficult-to-control worry and anxiety that causes physical symptoms, including restlessness, irritability, sleep disturbance, and difficulty concentrating. Panic disorder is characterized by recurrent panic attacks, which are defined as periods of intense fear of abrupt onset. OCD manifests as either obsessions (recurrent, intrusive, and inappropriate thoughts) or compulsions (repetitive behaviors) that are unreasonable, excessive, and cause much distress to the patient. PTSD is a response to a severe traumatic event in which the patient suffers fear, helplessness, or horror. A phobia is an irrational fear that causes a conscious avoidance of a situation, subject, or activity. **Patients with anxiety disorders are at high risk for developing comorbid depression.**

Bereavement

Bereavement is defined as symptoms of a major depressive episode that occur after the loss of a loved one. If the symptoms last longer than 2 months and involve suicidal ideations, morbid preoccupations, or psychosis, then a diagnosis of major depression is made.

Bipolar Disorder (Manic Depression)

This mood disorder affects genders equally but often presents in young people. Symptoms include the abrupt onset of increased energy, decreased need for sleep, pressured speech, decreased attention span, hypersexuality, spending large amounts of money, and engaging in outrageous activities. Concomitant substance abuse should always be investigated. Episodes must last longer than 1 week and should be abrupt, not continuous. Continuous behavior of this type suggests personality disorders or schizophrenia. A single episode of mania is sufficient for the diagnosis of bipolar disorder. **All patients diagnosed with depression should be questioned about mania,** as the treatments are different. Bipolar disorder is typically treated with mood stabilizers, which include valproate, carbamazepine, and lithium. The use of antidepressant agents in bipolar disorder may precipitate acute manic behaviors.

Dysthymic Disorder

This mood disorder presents with continuous low mood as the primary symptom. Typically 2 years of low mood is used for diagnosis. Dysthymia is less acute but longer in duration than major depression. If a major depressive episode takes place during the 2 years of dysthymia, then, by definition, it is major depression rather than dysthymia.

Comprehension Questions

25.1 A 62-year-old man presents for a follow-up visit for severe depression. His symptoms have included crying episodes, insomnia, and decreased appetite. He has suicidal ideations and states that he has a gun in his home. He has had auditory hallucinations, saying he hears a voice telling him that his wife is the devil. His symptoms have not been relieved by maximum doses of sertraline (Zoloft), venlafaxine (Effexor), or citalopram (Celexa). He is currently taking duloxetine (Cymbalta), which has also failed to improve his symptoms. Which of the following would most likely provide the quickest relief of his symptoms?

A. Electroconvulsive therapy (ECT)
B. Bupropion (Wellbutrin)
C. Stopping duloxetine and starting on a MAO inhibitor
D. Behavioral modification

25.2 A 40-year-old woman sees you in follow-up of treatment for recurrent depression. Her symptoms are improved a little after 2 months of fluoxetine [Prozac] 10 mg a day and weekly counseling sessions with a psychologist. She is having no medication side effects and both she and her husband state that she is taking her medication regularly. Which of the following would be the most appropriate next step?

A. Continue with your current plan and give it more time.
B. Increase the fluoxetine dose to 20 mg daily and continue counseling.
C. Discontinue fluoxetine and start paroxetine 10 mg daily.
D. Continue fluoxetine and add bupropion as adjunctive therapy.
E. Discontinue medications and arrange for psychiatric consultation for ECT.

25.3 Three weeks after starting a 22-year-old man on an SSRI for a first episode of depression, you receive a call from his mother stating that he hasn't slept in days, is speaking very rapidly, and has maxed-out his credit card buying electronic equipment. Which of the following is the most likely explanation for this situation?

A. He is having a medication side effect.
B. He is secretly taking too much of his SSRI.
C. His SSRI has unmasked an underlying bipolar disorder.
D. His SSRI has precipitated a hyperthyroid state.

ANSWERS

25.1 **A.** This patient has psychotic depression with suicidal ideations and has not responded to maximum doses of several antidepressants. He is more likely to respond to electroconvulsive therapy than to counseling or a change in medication.

25.2 **B.** The most common causes of treatment failure or poor response to therapy are inadequate medication dosing, inadequate length of treatment, or noncompliance. In this setting, where the patient is compliant and has had adequate time for response, increasing the dose of medication from 10 mg (a low starting dose) to 20 mg would be your first step. Typically, antidepressant medication dosages can be increased after 4 weeks of treatment if the response is inadequate.

25.3 **C.** In bipolar patients, the use of an SSRI can precipitate a manic state. It is critically important to assess for a history of manic episodes prior to starting antidepressant therapy. In some cases, bipolar disorder may initially present as major depression, so the institution of antidepressant medication may unmask an undiagnosed bipolar condition. Another condition to assess for in this situation is the concomitant use of recreational drugs, such as cocaine or methamphetamine.

Clinical Pearls

- While diagnosing depression rule out other medical diagnoses such as hypothyroidism, anemia, or infectious processes that could mimic some symptoms of depression.
- Always investigate the use of alcohol and drugs when evaluating for mood disorders.
- Suicidal and homicidal ideations should always be investigated and appropriately addressed when diagnosing depression.
- The addition of any new medication should be investigated to ensure it is not contributing to the patient's symptoms.

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Case 26

A 26-year-old G1P1001 woman presents for a routine postpartum visit 6 weeks following the vaginal delivery of a 7-lb baby girl. She had an uncomplicated prenatal course. She went into labor spontaneously at 39 2/7-week gestation. Her labor was augmented with oxytocin (Pitocin). The first stage of labor lasted for 9 hours, the second stage for 45 minutes, and the third stage for 15 minutes. She had a second-degree episiotomy that was repaired without difficulty. She started breast-feeding her baby immediately after delivery. Her postpartum course was uncomplicated and she was discharged from the hospital on the second postpartum day. She is exclusively breast-feeding her baby and reports that it is going well. She says that she felt "stressed, sad, and overwhelmed" during her first week at home, but that those feelings resolved after a week or so. She is now in excellent spirits and has strong support at home from her husband and her mother. She had some light vaginal bleeding that stopped about a week after delivery. She had a mild, white discharge for a couple of weeks that has also stopped and has had no vaginal discharge since. On examination, she appears well and has normal vital signs. Her general physical examination is normal. A pelvic examination shows a well-healed episiotomy, no cervical or vaginal discharge, and no cervical motion tenderness. Her uterus is normal size, firm, and nontender, and there are no adnexal masses.

- What are the maternal benefits of breast-feeding?
- The patient had been using a diaphragm for contraception prior to her pregnancy and wishes to use one again. What counseling should be given?
- She desires hormonal contraception. Which type is most recommended for a patient like her?

ANSWERS TO CASE 26:
Postpartum Care

Summary: A 26-year-old first-time mother presents for a routine, 6-week postpartum examination. She is breast-feeding her baby. Her examination is normal. She had a brief period in which she felt sad and overwhelmed, but this has resolved. She requests counseling about contraception.

- **Maternal benefits of breast-feeding:** Along with benefits to the baby, the maternal benefits include (but are not limited to) a more rapid return of uterine tone with reduced bleeding and a quicker return to nonpregnant size; a more rapid return to prepregnancy body weight; a reduced incidence of ovarian and breast cancer; the convenience of always having a readily available feeding supply for baby; and lower cost (no need to purchase formula).
- **Counseling regarding use of diaphragm:** There is no contraindication to using a diaphragm but she should have a new fitting.
- **Recommended hormonal contraception:** In breast-feeding women, the progestin-only "minipill" is recommended, as combined hormonal contraceptives can interfere with milk supply.

ANALYSIS

Objectives

1. Know the normal changes that occur in the postpartum period.
2. Be familiar with the diagnosis and management of common postpartum complications.
3. Be able to counsel patients on common postpartum issues such as contraception, breast-feeding, and postpartum depression.

Considerations

The postpartum period is defined as the time starting after the delivery of the placenta and lasting for 6 to 12 weeks. The postpartum period is a time of great change for the woman and the family. There are numerous normal physiologic changes that occur during the change from the pregnant to the nonpregnant state. Just as important are the many personal, social, and family changes that occur, which can be magnified for first-time parents or when there are unforeseen complications.

The immediate postpartum period, while still in the delivery suite, is usually focused on the medical conditions of both the neonate and the mother. The delivery attendant examines the mother, repairs any lacerations or episiotomy, and monitors for complications, such as postpartum hemorrhage. Simultaneous to this, the neonate is assessed and cared for during her initial transition to extrauterine life. The baby is often quite alert during this time, making it an ideal time to start breast-feeding efforts.

A typical postdelivery hospital stay is 24 to 48 hours for an uncomplicated vaginal delivery and 72 to 96 hours for a cesarean delivery. This time allows for recovery from the delivery or surgery, allows further monitoring for both maternal and neonatal problems, and can be used to provide education and support for the new mother and family. Typical maternal problems that occur during this time frame include pain, bleeding, lactation problems, and urinary difficulties (infections, incontinence, and retention). Postpartum fever is most often a sign of endometritis (infection of the uterus), but can also be caused by urinary tract or wound infections, thromboembolic disease, and mastitis.

The time following discharge from the hospital and for the subsequent 6 to 12 weeks usually represents the period of greatest adjustment. There are normal changes that occur, along with many potential medical and emotional complications. Future family planning and contraceptive issues often need to be addressed as well. A 6-week postpartum examination is usually scheduled, but many of the issues that can occur during this time frame should be addressed prior to discharge from the hospital.

APPROACH TO
Postpartum Care

DEFINITIONS

ENDOMETRITIS: A polymicrobial infection of the endometrium of the uterus, usually caused by ascending infection from the vagina.

LOCHIA: Yellow-white discharge, consisting of blood cells, decidual cells, and fibrinous products, that occurs following delivery.

CLINICAL APPROACH

Normal Changes

Immediately following delivery, the uterus begins the process of involution, the return to its nonpregnant size. Contraction of the uterine musculature promotes hemostasis by compressing the uterine blood vessels. An IV infusion of oxytocin (Pitocin) given during or immediately after the third stage of

labor will aid in producing increased uterine tone. Early breast-feeding also leads to uterine contraction, further promoting involution. In most cases, the uterus has returned to normal size by the time of the 6-week follow-up visit.

Vaginal bleeding is usually heaviest in the hours following delivery, then decreases significantly. Brown or blood-tinged lochia occurs for about the next week. This is followed by white or yellow lochia, which continues for approximately 3 to 6 more weeks. **In women who are not breast-feeding, menstruation usually restarts by the third postpartum month.** In women who are breast-feeding, ovulation and menstruation can be suppressed for much longer. Anovulation will persist for longer periods of time in women who exclusively breast-feed their babies.

Breast engorgement, signaling increased milk production, typically occurs 1 to 4 days after delivery. In breast-feeding women, this is best managed by increased frequency of feedings. In women who are not breast-feeding, the use of ice packs, supportive bras, and nonsteroidal anti-inflammatory drugs (NSAIDs) can reduce discomfort.

MEDICAL COMPLICATIONS

Hemorrhage

Postpartum hemorrhage is categorized as "early" or "late," depending on when the hemorrhage began. Early postpartum hemorrhage occurs within 24 hours of delivery, most often immediately postpartum; late postpartum hemorrhage occurs between 24 hours and 6 weeks after delivery. The causes of most cases of postpartum hemorrhage can be remembered with the mnemonic "The Four Ts" (Table 26–1). Careful examination focused on the likely causes should be performed promptly to identify the source of the bleeding.

As with all emergency situations, the **first priority in this setting is assessment of the ABCs—airway, breathing, and circulation.** It is important to ensure that adequate IV access is available, preferably two large-bore IV catheters. Fluid resuscitation with a crystalloid solution (normal saline, lactated Ringer solution) should be given as necessary and massive hemorrhage may require transfusion with packed red blood cells.

Table 26–1 THE FOUR Ts OF POSTPARTUM HEMORRHAGE

Tone	Uterine atony
Trauma	Cervical, vaginal, or perineal lacerations; uterine inversion
Tissue	Retained placenta or membranes
Thrombin	Coagulopathies

Uterine atony is the most common cause of postpartum hemorrhage. Failure of the uterus to contract adequately results in continued bleeding from uterine vasculature. Risks include prolonged labor, prolonged use of oxytocin during labor, a large baby, and grand multipara (five or more previous children). **Initial management of uterine atony includes the IV administration of oxytocin and initiation of bimanual uterine massage.** When these fail to control the bleeding, methylergonovine (Methergine) may be given intramuscularly. **Methylergonovine is contraindicated in patients with hypertension**, as it may cause an abrupt increase in blood pressure. If the bleeding continues following this, or if the patient is hypertensive, prostaglandin F_{2a} (Hemabate) can be injected intramuscularly or intramyometrially. Prostaglandin F_{2a} is contraindicated in women with asthma. Misoprostol (Cytotec), given rectally or orally, is another option to increase uterine tone in the setting of postpartum hemorrhage.

Fever

Postpartum fever, especially if associated with uterine tenderness and foul-smelling lochia, is often a sign of endometritis. Endometritis complicates approximately 10% of cesarean and 1% to 2% of vaginal deliveries. Antibiotics given prophylactically during a cesarean delivery can reduce the risk of this complication. When it does occur, endometritis should be treated with broad-spectrum antibiotics that cover vaginal and gastrointestinal flora.

Urinary tract infections (UTI) are another common cause of fever after both vaginal and cesarean deliveries. Urinary frequency, urgency, and burning are typical presenting symptoms. Catheterization of the urinary bladder, which occurs routinely during a cesarean delivery and frequently during vaginal deliveries, raises the risk of introducing bacteria into the normally sterile environment of the bladder.

Other causes of fever in the postpartum period, especially in women delivered by cesarean, are identical to causes of fever in other postsurgical patients. These include atelectasis, wound infections, and venous thromboembolic disease.

Mood Disorders

Up to three-fourths of women develop some type of psychological reaction following the delivery of a child. In most cases, the symptoms are mild and self-limited. However, a smaller but significant percentage can have a reaction of such severity as to require medical or psychiatric intervention.

Approximately 30% to 70% of women develop a temporary state known as the **"maternity blues"** or "baby blues." This condition **develops within the first week after delivery and typically resolves by the 10th postpartum day.** Symptoms include tearfulness, sadness, and emotional lability. The etiology is not entirely clear, but may be multifactorial and include both hormonal changes following delivery along with components of stress, sleep deprivation, and adjustment to the new role of mother. Postpartum depression occurs following 10% to 20% of

pregnancies and can occur following gestations of any length— term, preterm, miscarriages, or abortions. The onset is defined as occurring within 4 weeks postpartum, but it has been seen up to a year later. **The symptoms of postpartum depression are the same as in major depression.** The severity can vary from mild to severe and suicidal. There is a **high recurrence rate in subsequent pregnancies** and an increased risk in women with a history of depression unrelated to pregnancy. Untreated, postpartum depression can last for 6 months or more and can be a significant cause of morbidity. All women should be screened for a history of psychiatric disorders during their prenatal care and should be questioned about symptoms of depression during postpartum visits. The **treatment is similar to the treatment of nonpregnancy-related depression.** Women who are a risk to themselves, or to others, or who are unable to care for themselves should be admitted to the hospital. Selective serotonin reuptake inhibitors (SSRIs) are first-line therapy because of their efficacy and safety. They also are considered safe in breast-feeding. Counseling and general supportive measures at home are also important adjuncts to treatment.

Postpartum psychosis is a rare, but potentially devastating, complication following pregnancy. Manic or frankly delusional behaviors may present within a few days to a few weeks of delivery in up to 1 in 1000 postpartum patients. All women with postpartum psychosis should be hospitalized and comanaged with a psychiatrist. Without proper treatment, there is a high risk of suicide and infanticide associated with this diagnosis.

BREAST-FEEDING

Counseling and encouragement regarding both the maternal and infant benefits of breast-feeding should start during the prenatal period. Neonatal benefits include ideal nutrition, increased resistance to infection, and a reduced risk of gastrointestinal difficulties. Maternal benefits include improved mother–child bonding, more rapid uterine involution, quicker return to prepregnant body weight, convenience, decreased costs, and long-term reduced risks of ovarian and breast cancer. Breast-feeding promotion and education can increase the rate of breast-feeding and the duration for which women breast-feed their babies.

Women should be allowed to nurse their newborns as soon as possible following delivery. During this time, the newborns are often very alert and have strong rooting and sucking reflexes, which promote latching on to the nipple. Initial feedings provide colostrum, an antibody-rich clear/yellow nourishment for the newborn. Breast engorgement and milk letdown commonly occurs between the second and fourth postpartum days.

There are few contraindications to breast-feeding. HIV infection is a contraindication, as vertical transmission can occur through infected breast milk. Most mothers with hepatitis B and C can safely breast-feed, although women with acute, active hepatitis B infection should not breast-feed. Women who have had breast-reduction surgery with nipple transplantation will be unable to breast-feed.

Common maternal complications of breast-feeding include sore or cracked nipples and mastitis. Sore nipples can be managed with frequent position changes, alternating breasts during feedings, and applications of lanolin. Mastitis, an obstruction of milk glands sometimes secondarily infected with bacteria, is treated by increased nursing or breast pumping and oral antibiotics, such as cephalexin or dicloxacillin. Mastitis should not result in discontinuation of nursing.

FAMILY PLANNING

Most women resume sexual activity by 3 months postpartum. Numerous options are available to women for contraception and family planning. Discussion of these options ideally should occur in the prenatal period and again before discharge from the hospital.

Oral contraceptive pills (OCPs) are the most widely used reversible form of contraception. Available OCPs contain either combined estrogen and progestin or are progestin only. **In breast-feeding women, the progestin-only pills are preferred** because the combination OCPs might reduce lactation. Both the American College of Obstetricians and Gynecologists and the World Health Organization recommend waiting for 6 weeks postpartum to start oral contraceptives in breast-feeding women. Injectable long-acting depot medroxyprogesterone (Depo-Provera) may also be used in breast-feeding women and should also be given at least 6 weeks postpartum. **Non–breast-feeding women should wait 3 weeks after delivery to start combined OCPs,** as the risk of thromboembolic disease is higher in those who start at earlier times.

Barrier methods of contraception may also be used regardless of breast-feeding status. An intrauterine device (IUD) may be placed at the 6-week postpartum visit; earlier placement is associated with an increased rate of expulsion of the device. **Diaphragms and cervical caps can be used, but should be refitted at the 6-week visit** to ensure an appropriate fit.

Lactation-induced amenorrhea provides a high level of natural contraception in the first 6 months postpartum. Women who breast-feed exclusively and who are amenorrheic have a 98% contraceptive protection for 6 months. After 6 months, if menses restart, or if breast-feeding is reduced, the risk of pregnancy increases and alternate forms of contraception should be used.

Comprehension Questions

26.1 You are called by the postpartum nurse to see a 20-year-old woman who delivered an 8 lb 9 oz baby boy approximately 6 hours ago. The nurse noted that the patient is continuing to bleed more than expected. The patient is awake and talking, but feels dizzy. Her blood pressure is 90/40 mm Hg and her pulse is 110 bpm. You see that her perineal pad is soaked with blood. Which of the following is your most appropriate initial intervention?

A. Add 20 units of oxytocin (Pitocin) to the IV of 0.45% saline that is currently running at 125 mL/h.
B. Perform bimanual uterine massage.
C. Place a large-bore IV and give a 1 L bolus of 0.9% saline.
D. Give an IM injection of methylergonovine (Methergine).

26.2 A 29-year-old first-time mother comes to you for her routine 6-week postpartum visit. Her husband, who accompanied her to the visit, reports that his wife is tearful much of the time. She has not been sleeping well, has little energy, and a reduced appetite. She denies any suicidal thoughts, hallucinations, or feelings that she wants to harm her baby. Which of the following is the most appropriate intervention?

A. Reassurance that these feelings will pass within a week or so
B. Referral to a psychiatrist for outpatient management
C. Institution of SSRI therapy and close follow-up
D. Admission to the hospital and urgent psychiatric consultation

26.3 You see a 30-year-old woman for an acute visit 16 days postpartum. She has been nursing her baby daughter, but has developed a very sore left breast. On examination, the patient has a temperature of 101.3°F (38.5°C). The breast is diffusely tender but primarily in the upper inner quadrant. The skin overlying the area of most tenderness is erythematous and warm. There is no nipple discharge and the remainder of the examination is normal. Which of the following is the best treatment?

A. This condition is self-limited, but she should stop nursing the baby on the left breast until this condition resolves.
B. She may nurse from the unaffected breast, but should simply pump and discard the milk from the painful breast.
C. The patient should receive oral dicloxacillin.
D. She should have a fine needle aspiration.

26.4 A 19-year-old woman is seen in the office 3 weeks postpartum. She is exclusively breast-feeding and has not had a menstrual cycle since her delivery. She would like to have an IUD placed for contraception, as she would like to wait several years before having another baby. Which of the following actions would be most appropriate at this time?

A. Plan to insert the IUD at a 6-week postpartum visit.
B. Prescribe progestin-only minipills until she is no longer breastfeeding and then insert the IUD.
C. Advise that she needs no contraception until she is no longer breastfeeding and she should return after that time for the IUD.
D. Insert the IUD today.

ANSWERS

26.1 **C.** This patient is symptomatically hypovolemic, with dizziness, hypotension, and tachycardia. Fluid resuscitation must be your first intervention—remember the ABCs first! Once you have started the management of this critical issue, you should turn your attention to identifying and correcting the source of the bleeding.

26.2 **C.** This is a picture of postpartum depression. The symptoms are identical to those of a major depressive episode. The maternity blues is a self-limited condition that starts in the first postpartum week and resolves in the second. Fortunately, this patient does not have signs of postpartum psychosis—mania, hallucinations, and delusions. Appropriate management includes the use of an SSRI, counseling, and close follow-up.

26.3 **C.** Mastitis is a common complication of breast-feeding. It is caused by gland obstruction and sometimes, as in this case, there also are signs of infection. Treatment is directed at relieving the obstruction, so increased breast-feeding or pumping is helpful. The antibiotics typically used for this complication are considered safe to use while nursing. Cephalexin or a penicillin-based antibiotic would be appropriate in this case.

26.4 **A.** IUDs provide highly effective, reversible contraception and are very useful for women who wish to space out pregnancies for several years. Postpartum insertion prior to 6 weeks is associated with a higher risk of expulsion of the IUD from the uterus as it involutes. Breastfeeding-induced amenorrhea provides a high degree of protection against pregnancy for about the first 6 months postpartum, but an alternate form of contraception should be used after 6 months or when menses restart.

Clinical Pearls

- Many of the important postpartum issues—mood problems, contraception, and breast-feeding—are best managed by addressing them in the prenatal course first, and then readdressing or reinforcing them in the postpartum period.
- Most causes of postpartum hemorrhage can be remembered with the four Ts: tone, trauma, tissue, and thrombin.

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Case 27

A 66-year-old woman presents to your office complaining of shortness of breath and bilateral leg edema that have been worsening for 3 months. She emphatically tells you, "I get out of breath when I do housework and I can't even walk to the corner." She has also noticed difficulty sleeping secondary to a dry cough that wakes her up at night and further exacerbation of her shortness of breath while lying flat. This has forced her to use three pillows for a good night's sleep. She denies any chest pain, wheezing, or febrile illness. She has no past illnesses and takes no medications. She's never smoked and drinks socially. On examination, her blood pressure is 187/90 mm Hg, her pulse is 97 bpm, her respiratory rate is 16 breaths per minute, her temperature is 98°F (36.6°C), and her oxygen saturation is 93% on room air by pulse oximetry. She has a pronounced jugular vein. Cardiac examination reveals a pansystolic murmur. Examination of her lung bases produces dullness bilaterally. You find 2+ pitting edema of both ankles. An ECG shows a normal sinus rhythm and a chest x-ray demonstrates mild cardiomegaly with bilateral pleural effusions. You decide she needs further workup, so you call the hospital where you have admitting privileges and arrange for a telemetry bed.

- What is the most likely diagnosis?
- What is the next diagnostic step?
- What is the initial step in therapy?

ANSWERS TO CASE 27:
Congestive Heart Failure

Summary: A 66-year-old woman presents to your office with worsening shortness of breath, bilateral leg edema, and three-pillow orthopnea. She is not known to be hypertensive, but her blood pressure (BP) is 187/90 mm Hg and she is only saturating 93% on room air. Her examination reveals jugular venous distension (JVD), a cardiac murmur, and decreased breath sounds at both lung bases. On a chest x-ray you find bilateral pleural effusions and decide to admit her for further workup and management.

- **Most likely diagnosis:** New-onset congestive heart failure.
- **Next diagnostic step:** Serial cardiac enzymes and ECGs; blood work to include a CBC, electrolytes, and renal function; echocardiogram.
- **Initial therapy:** Telemetry monitoring, IV diuretics, and oxygen.

ANALYSIS

Objectives

1. Know how to clinically recognize congestive heart failure (CHF).
2. Understand the classification of CHF.
3. Understand the mechanism of action of the drugs used in the treatment of acute and chronic CHF.
4. Understand the underlying pathophysiology that occurs in CHF and the rationale for treatment options.
5. Be familiar with the outpatient management of CHF and the importance of patient education.

Considerations

This 66-year-old woman presented with congestive heart failure. Her most immediate problem is oxygenation and volume overload on her weakened heart. The **first priority is optimizing oxygen exchange** by administering oxygen via nasal cannula, dilating pulmonary vasculature, and decreasing cardiac preload and afterload. Most cases of CHF are caused by either coronary artery disease or hypertension, so it is imperative to admit these patients for serial cardiac enzymes and further assessment of heart function. The overloading of fluid in the lungs is a common cause of anxiety and distress in patients with acute CHF because of the continuous struggle to oxygenate adequately. This anxiety

activates sympathetic pathways and mounts catecholamine-induced responses, which produce further worsening of acute heart failure by causing tachycardia and increasing peripheral vascular resistance, leading to greater stress on the heart and worsening of symptoms. These triggers can, in part, be suppressed by the use of an agent such as morphine sulfate, which acts as both an anxiolytic and a vasodilator. Furosemide (Lasix) is the diuretic of choice, not only for its diuretic effect but also for its immediate vasodilatory action on bronchial vasculature. Admitting these patients to the hospital allows for closer maintenance of homeostasis in their fluid balances and evaluation of any underlying condition that may have precipitated the CHF. Other medications, including angiotensin-converting enzyme (ACE) inhibitors and β-blockers, help to control heart failure symptoms by decreasing preload and afterload, and reducing cardiac remodeling.

APPROACH TO
Congestive Heart Failure

DEFINITIONS

CONGESTIVE HEART FAILURE: Imbalance in pump function where the heart fails to maintain the circulation of blood adequately.

FRAMINGHAM HEART STUDY: Large, prospective cohort study of the epidemiologic factors associated with cardiovascular diseases.

CLINICAL APPROACH

CHF is divided into two main categories: systolic and diastolic dysfunction. Systolic dysfunction exists when there is a dilated left ventricle with impaired contractility. Diastolic dysfunction occurs in a normal or intact left ventricle that has an impaired ability to relax, fill, and eject blood. Table 27–1 lists the findings frequently associated with CHF.

Dyspnea on exertion is the most sensitive symptom for the diagnosis of CHF, but its specificity is much lower. Other symptoms, which are common but less sensitive for the diagnosis, include dyspnea at rest, anxiety, orthopnea, paroxysmal nocturnal dyspnea, and cough productive of pink, frothy sputum. Nonspecific symptoms sometimes reported are weakness, lightheadedness, abdominal pain, malaise, wheezing, and nausea. Patients may have a medical history of hypertension, coronary artery disease, or other heart diseases (eg, cardiomyopathy, valvular disease). Histories of cigarette smoking and alcohol abuse may also be found.

Table 27–1 ETIOLOGIES OF HEART FAILURE

FINDING	COMMON CAUSES
Cardiac rhythm disorders	Complete heart block Supraventricular tachycardia Ventricular tachycardia Sinus node dysfunction
Volume overload	Structural heart disease (ventricular septal defect; patent ductus arteriosus; aortic or mitral regurgitation, complex cardiac lesions) Anemia Sepsis
Pressure overload	Structural heart disease (aortic or pulmonary stenosis; aortic coarctation) Hypertension
Systolic ventricular dysfunction or failure	Myocarditis Dilated cardiomyopathy Malnutrition Ischemia
Diastolic ventricular dysfunction or failure	Hypertrophic cardiomyopathy Restrictive cardiomyopathy

Etiologies

The symptoms and signs that occur are unique and characteristic of the alterations to the normal physiologic function. Symptoms of right-sided heart failure include venous congestion, nausea/vomiting, distension/bloating, constipation, abdominal pain, and decreased appetite. Common signs of right-sided heart failure are fluid retention, weight gain, peripheral edema, JVD, hepatojugular reflux, hepatic ascites, and splenomegaly.

Left-sided heart failure manifests with pulmonary congestion, resulting in the symptoms of dyspnea on exertion, paroxysmal nocturnal dyspnea, orthopnea, wheezing, tachypnea, and cough. The signs of pulmonary congestion are bilateral pulmonary rales, S_3 gallop rhythm, Cheyne-Stokes respiration, pleural effusion, and pulmonary edema. Pulmonary edema is often the first manifestation of congestive heart failure, but it can also be caused by a variety of noncardiac conditions (Table 27–2).

Signs common to both left- and right-heart failure are tachycardia, cardiomegaly, cyanosis, oliguria, nocturia, and peripheral edema. Symptoms common to both include weakness, fatigue, confusion (delirium), decreased

Table 27–2 NONCARDIAC CAUSES OF PULMONARY EDEMA

Direct injury to lung	Chest trauma Aspiration Smoke inhalation Pneumonia Oxygen toxicity Pulmonary embolism
Hematogenous injury to lung	Sepsis Pancreatitis Nonthoracic trauma Leukoagglutination reactions Multiple transfusions IV drug use Cardiopulmonary bypass
Possible lung injury plus elevated hydrostatic pressures	High-altitude pulmonary edema Neurogenic pulmonary edema Reexpansion pulmonary edema

Data from Schwartzstein RM. Dyspnea and pulmonary edema. In: Fauci AS, Braunwald E, Kasper DL, et al, eds. *Harrison's Principles of Internal Medicine*. 17th ed. New York, NY: McGraw-Hill; 2008:224.

mental status, insomnia, decreased exercise tolerance, headache, stupor, coma, paroxysmal nocturnal dyspnea, and declining functional status.

After the Framingham Heart Study was reviewed, criteria were devised to help diagnose CHF by both signs and symptoms. Two major criteria or one major and two minor criteria can lead to a presumptive diagnosis of CHF. The major signs are paroxysmal nocturnal dyspnea, JVD, rales, cardiomegaly, pulmonary edema, S_3 gallop, central venous pressure greater than 16 cm H_2O, circulation time of 25 seconds, hepatojugular reflex, and weight loss of 4.5 kg over 5 days of treatment. Minor criteria include bilateral ankle edema, nocturnal cough, dyspnea on exertion, hepatomegaly, pleural effusions, decreased vital capacity by one-third of maximum, and tachycardia.

Epidemiology

Of the general population between the ages of 50 and 59 years, 1% to 2% will have CHF, but that number increases to 6% to 10% in persons older than age 65. Approximately 30% to 40% of patients with CHF are hospitalized every year; **it is the leading diagnosis-related group (DRG) among hospitalized patients older than age 65 years.** The 5-year mortality rate remained essentially unchanged from 1971 to 1991, at 60% in men and 45% in women. Data from the Framingham Heart Study shows a **median survival of 3.2 years for men and 5.4 years for women with CHF.** The most common cause of death is progressive heart failure,

but sudden death may account for up to 45% of all deaths. African Americans are 1.5 times more likely to die of CHF than are Whites. Nevertheless, African American patients appear to have similar or lower in-hospital mortality rates than White patients. The prevalence is greater in men than in women for patients ages 40 to 75 years; after the age of 75, however, there is no difference.

Evaluation

After an initial assessment of the "ABCs"—airway, breathing, and circulation—patients presenting with dyspnea suggestive of heart failure should be evaluated with a history, physical examination, and focused testing. The testing should be designed to confirm CHF (or lead to an alternate diagnosis), identify a cause, and assess the severity of the disease. These initial tests should include blood tests, radiographic studies, electrocardiography, and echocardiography.

Initial blood tests should generally include a complete blood count (CBC), serum electrolytes, renal function tests, hepatic function tests, and cardiac enzymes. A high white blood cell count can help to identify the presence of an underlying infection, a common triggering event of CHF. Anemia is another common trigger of CHF. In an anemic patient, the oxygen-carrying ability of the blood is reduced. The cardiac output must increase to compensate for this. If the anemia is mild, or if the heart is normal, this compensation may occur without producing symptoms; if the anemia is severe or if there is underlying cardiac abnormality (from previous ischemia, hypertension, valvular abnormality, etc), heart failure may occur.

Electrolyte abnormalities are common in the presence of CHF. Neurohumoral responses to a failing heart result in water and sodium retention and potassium excretion. Severe heart failure can result in a dilutional hyponatremia. Medications used by patients with chronic heart disease (diuretics, ACE inhibitors, others) also can lead to electrolyte abnormalities. Increased vascular congestion can lead to passive congestion of the liver, resulting in increases in serum transaminases. Severe CHF can lead to jaundice as a consequence of impaired hepatic function caused by congestion. Serial measurement of cardiac enzymes is necessary to evaluate for the presence of acute myocardial infarction as the inciting event.

One of the neurohumoral responses to the presence of a failing ventricle is release of brain natriuretic peptide (BNP). The "Breathing Not Properly" study, published in 2004, showed that elevated levels of BNP and its prohormone (pro-BNP) can be used to assist in the diagnosis of CHF as a cause of acute dyspnea. Elevated levels of BNP and pro-BNP are a sensitive and specific marker for the diagnosis of CHF. In a dyspneic patient, a level of BNP less than 100 pg/mL suggests that the symptoms are unlikely to be caused by CHF; a BNP level less than 500 pg/mL is consistent with the diagnosis of CHF.

ECG findings in CHF are variable. An ECG is useful to evaluate for evidence of acute ischemia or arrhythmia as cause of the CHF and can also reveal the presence of ventricular hypertrophy, often seen in chronic hypertension. Chest x-ray can also show cardiomegaly and cardiac chamber enlargement. Typically, the cardiothoracic ratio is greater than 50%. One of the earliest chest x-ray findings in CHF is cephalization of the pulmonary vasculature. As the failure progresses, interstitial pulmonary edema can be seen as perihilar infiltrates, often in a butterfly pattern. Pleural effusions can also be found. Effusions are usually bilateral but, if unilateral, are more often seen on the right hemithorax than the left.

Echocardiography is the gold-standard diagnostic modality in the presence of CHF. It may help to identify regional or global wall motion abnormalities, cardiomyopathy, ventricular or septal hypertrophy, and cardiac ejection fraction. It also can find cardiac tamponade, pericardial constriction, and pulmonary embolus. Echocardiography also is useful in identifying valvular stenosis or regurgitation, either of which can lead to heart failure. These findings aid in the determination of whether the heart failure is a systolic or diastolic dysfunction, an important distinction in the decision of appropriate treatment.

Classification of CHF

CHF severity is characterized by the symptoms a patient has and the degree that the symptoms limit a patient's lifestyle. There are several classification systems in use; two of the most widely used are the New York Heart Association (NYHA) and the American Heart Association (AHA) classifications. Table 27–3 summarizes these systems. The classification of CHF is important in determining the appropriate treatment and prognosis for the patient.

Management of Heart Failure

In all cases of acute CHF, **the initial management imperative is the "ABCs"**—airway, breathing, and circulation. Supplemental oxygen, initially 100% via non-rebreather face mask, should be administered. If necessary, ventilation can be assisted with continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP), or mechanical ventilation. Cardiac and continuous pulse oximetry monitors should be placed and IV access obtained.

When acute pulmonary edema caused by CHF is diagnosed, the next step in management is the administration of a loop diuretic. Furosemide is generally the treatment of choice, both for its potent diuretic effect and for its rapid bronchial vasculature vasodilation. Nitrates, particularly nitroglycerin when given IV, reduce myocardial oxygen demand by reducing preload and afterload. Nitroglycerin also can rapidly reduce blood pressure and is the treatment of choice in a patient who has CHF and whose blood pressure is elevated.

Table 27–3 CLASSIFICATION OF SEVERITY OF CONGESTIVE HEART FAILURE

AMERICAN HEART ASSOCIATION	NEW YORK HEART ASSOCIATION	LIMITATIONS	SYMPTOMS
A	—	None	Risk factors
B	I	None with normal activities	Left ventricular dysfunction
B	II	Mild	Fatigue, dyspnea with normal activities
C	III	Moderate	Activities of daily living
D	IV	Severe	At rest

It should be used with caution or avoided in a hypotensive patient. IV morphine sulphate can be an effective adjunct to therapy. Along with its analgesic and anxiolytic properties, morphine is a venodilator (primary effect) and arterial dilator, resulting in a reduction in preload and an increase in cardiac output.

Most patients who present to the emergency department with symptomatic CHF will require admission to a telemetry unit for treatment and monitoring. Discharge criteria from the emergency department includes the gradual onset of symptoms, rapid resolution of symptoms with treatment, oxygen saturation of >90% on room air, and exclusion of an acute coronary syndrome as the cause of the CHF.

Outpatient Management of CHF

Patient education is an important aspect of the care for all patients with CHF. All patients should be advised about the importance of dietary sodium and fluid restriction. A normal American diet contains 6 to 10 g sodium chloride a day; initial restriction in patients with CHF should be 2 to 4 g/d. Stricter restrictions may be necessary in those with more severe disease. Overweight and obese patients should be counseled on appropriate caloric restrictions and encouraged to exercise to reduce weight. The importance of strict management of blood pressure and modification of other cardiac risk factors should be emphasized as well.

ACE inhibitors should be considered first-line therapy in patients with CHF and reduced left ventricular function. ACE inhibitors reduce preload,

afterload, improve cardiac output, and inhibit tissue renin–angiotensin systems. The result of this is an improvement in symptoms and a reduction in mortality. ACE inhibitors can also delay the development of symptomatic CHF in asymptomatic patients with a reduced cardiac ejection fraction. Angiotensin receptor blockers (ARBs) can be used in place of an ACE inhibitor in a patient who does not tolerate an ACE inhibitor because of side effects (eg, cough).

ACE inhibitors are contraindicated in pregnancy, hypotension, hyperkalemia, and bilateral renal artery stenosis, and should be used with caution in patients with renal insufficiency.

For many years, the teaching was to avoid the use of β-blockers in the setting of CHF. However, more recent data support the use of β-blockers for both systolic and diastolic heart failure. **The administration of β-blockers, especially in high doses, in the setting of acute CHF, can worsen symptoms;** consequently, initial doses should be low and titrated up over several weeks. β-Blockers can reduce the sympathetic tone and the cardiac muscle remodeling associated with chronic heart failure. β-Blockers reduce mortality in patients with an ejection fraction of less than 35% and are primarily indicated in patients with NYHA Class II or III heart failure, or in patients with coronary artery disease.

Diuretics should be used to reduce fluid overload in both the acute and chronic settings. Loop diuretics (furosemide, bumetanide, torsemide, ethacrynic acid) can be used in all stages of CHF and are useful in pulmonary edema and refractory heart failure. Thiazide diuretics (hydrochlorothiazide, chlorthalidone, others) are used in mild heart failure and may be used in combination with other diuretics in more severe CHF. Diuretic doses can be adjusted based on daily weight measurements by the patient.

The aldosterone antagonist spironolactone reduces mortality in advanced heart failure. It also functions as a diuretic and should be considered in NYHA Class III and IV heart failure. Patients on this medication must be closely monitored for the development of hyperkalemia, which can become profound and lead to arrhythmia.

Calcium channel blockers, in general, are contraindicated in systolic heart failure, because they increase mortality. The exception to this is the dihydropyridine calcium channel blocker amlodipine (Norvasc), which did not increase or decrease mortality. Nondihydropyridine calcium channel blockers (diltiazem, verapamil) are useful in heart failure caused by diastolic dysfunction, as they promote increased cardiac output by lowering heart rate, which allows for more ventricular filling time.

Approximately one-third of patients with NYHA Class III or IV heart failure and reduced ejection fraction have ECG evidence of abnormal ventricular conduction (ie, prolonged QRS duration). These patients can be helped by promoting synchronous contraction of both the right and left ventricles using a biventricular pacemaker. This process, also known as **cardiac resynchronization therapy**, has been shown to reduce mortality and hospitalization in patients with symptomatic CHF in spite of maximal medical therapy.

Comprehension Questions

27.1 A 57-year-old man who has known New York Heart Association Class II Heart Failure presents to clinic after noting to become dyspneic with significant exertion. On physical examination his BP is 140/86 mm Hg, pulse 86 bpm, and respiratory rate 20 breaths per minute. A 2/6 pansystolic murmur is best heard at the right sternal border. There is no JVD but 1+ pretibial and pedal edema are noted. He currently takes an ACE inhibitor and aspirin. Which one of the following additional medications have been shown to improve longevity in this situation?

A. Warfarin (Coumadin)
B. Digitalis
C. β-Blocker
D. Nondihydropyridine calcium channel blocker
E. Amiodarone (Cordarone)

27.2 A 52-year old man with a long-standing history of marginally controlled hypertension presents with gradually increasing shortness of breath and reduced exercise tolerance with pain in his calves that causes him to stop walking after one block. His medications include enalapril and metoprolol. His physical examination reveals a blood pressure of 140/90 mm Hg, a respiratory rate of 22 breaths per minute, heart rate of 88 bpm, bibasilar rales, and trace pitting edema. Posterial tibial and Dorsalis pedis pulses are 1+. Which of the following diagnostic tests is most appropriate in the further evaluation of this patient?

A. Cardiac MRI
B. 12-lead ECG
C. Spiral CT
D. Two-dimensional echocardiography with Doppler
E. Posteroanterior and lateral chest radiographs

27.3 A 64-year-old man is noted to have congestive heart failure because of coronary artery disease. Over the past 2 days, he has developed progressive dyspnea and orthopnea. On examination, he is found to be in moderate respiratory distress, has JVD, and rales on pulmonary examination. He is diagnosed with pulmonary edema. Which of the following agents is most appropriate at this time?

A. Hydrochlorothiazide
B. Furosemide
C. Carvedilol
D. Spironolactone
E. Digitalis

27.4 A 70-year-old African American man with New York Heart Association Class III heart failure sees you for follow-up. He has shortness of breath with minimal exertion. The patient is adherent to his medication regimen. His current medications include lisinopril 40 mg twice daily, carvedilol 25 mg twice daily, and furosemide 80 mg daily. His blood pressure is 100/60 mm Hg, and his pulse rate is 70 bpm and regular. Physical examination findings include a few scattered bibasilar rales, an S_3 gallop, and no peripheral edema. An ECG reveals a left bundle branch block and echocardiography reveals an ejection fraction of 25%. Which of the following is the best next step for this patient?

A. Increase the furosemide dosage to 80 mg twice daily.
B. Refer for coronary angiography.
C. Increase the lisinopril dosage to 80 mg twice daily.
D. Increase the carvedilol dosage to 50 mg twice daily.
E. Refer for cardiac resynchronization therapy.

ANSWERS

27.1 **C.** β-Blockers are recommended to reduce mortality in symptomatic patients with heart failure. Because polypharmacy can reduce compliance, the role that digoxin plays in heart failure management is unclear. Calcium channel blockers should be used with caution in patients with heart failure because they can cause peripheral vasodilation, decreased heart rate, decreased cardiac contractility, and decreased cardiac conduction.

27.2 **D.** The most useful diagnostic tool for evaluating patients with heart failure is two-dimensional echocardiography with Doppler to assess left ventricular ejection fraction (LVEF), left ventricular size, ventricular compliance, wall thickness, and valve function. It should be performed during the initial evaluation. Chest radiography and 12-lead electrocardiography should be performed in all patients presenting with heart failure, but should not be used as the primary basis for determining which abnormalities are responsible for the heart failure.

27.3 **B.** Furosemide, a loop diuretic, is a first-line agent in CHF exacerbation with pulmonary edema. The other medications listed may be used in the management of CHF, but are not indicated in an acute exacerbation.

27.4 **E.** This patient is already receiving maximal medical therapy. The 2002 joint guidelines of the American College of Cardiology, the American Heart Association (AHA), and the North American Society of Pacing and Electrophysiology endorse the use of cardiac resynchronization therapy (CRT) in patients with medically refractory, symptomatic, NYHA Class III or IV disease with a QRS interval of at least 130 msec, a left ventricular end-diastolic diameter of at least 55 mm, and a left ventricular ejection fraction (LVEF) less than or equal to 30%. These guidelines were refined by an April 2005 AHA Science Advisory, which stated that optimal candidates for CRT have a dilated cardiomyopathy on an ischemic or nonischemic basis, an LVEF less than or equal to 35%, a QRS complex greater than or equal to 120 msec with sinus rhythm, and are NYHA functional Class III or IV despite maximal medical treatment for heart failure.

Clinical Pearls

- The initial hour in the management of a patient with either new-onset CHF or an acute exacerbation is crucial to their outcome.
- Simple measures, such as decreasing cardiac preload by sitting the patient up with their legs on the ground and their arms by their side, maintaining an airway and giving oxygen, and giving sublingual nitroglycerin, can alleviate CHF immediately.

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Case 28

A 38-year-old G3P3, divorced executive presents to your clinic for contraceptive advice. She is currently in a monogamous relationship and has been in it for several months. She denies any allergy. She occasionally drinks alcohol and smokes half a pack of cigarettes a day. She mentions that she used to take birth control pills without any problems. All of her three children were born via vaginal delivery without complication. She and her boyfriend are sexually transmitted disease (STD)-free based on their recent checkups. She reports that she is tired of using over-the-counter contraceptives because they are inconvenient. She said that her life is very busy because of work. She fears any form of surgery and has not excluded having another child. Her laboratory workup is normal. Her physical examination is normal. She is looking for the "best contraceptive method" for her situation.

- What contraceptive options are available to this woman?
- Which contraceptives are contraindicated for her?

ANSWERS TO CASE 28:
Family Planning—Contraceptives

Summary: A 38-year-old parous woman presents for counseling regarding her contraceptive options. She is in a monogamous relationship. She reports that she is dissatisfied with using over-the-counter options and that she is not ready for permanent sterilization. She smokes a half-pack of cigarettes daily.

- **Available contraceptive options:** Barrier contraceptives, intrauterine device, natural family planning.
- **Contraindicated contraceptive options:** Oral contraceptive pills.

ANALYSIS

Objectives

1. Know the available methods of contraception.
2. Be aware of contraindications for and the side effects of contraceptives.

Considerations

Choosing a method of contraception is a personal decision, based on individual preferences, medical history, and lifestyle. Each method of contraception has a number of risks and benefits of which the patient should be aware. In the United States, approximately 50% of pregnancies are unintended and approximately 50% of these pregnancies end in abortion. Each method of contraceptive has a failure rate, which is an inability to prevent pregnancy over a 1-year period. Sometimes the failure rate is a result of the method and sometimes it is a result of human error. Each method has possible side effects. Some methods require lifestyle modifications. Patients with certain medical conditions cannot use certain types of contraceptives.

There are numerous contraceptive options available and recommendations regarding contraceptive use must be individualized. In the case given, there are several important factors that must be considered. Hormonal contraceptives are contraindicated in women older than age 35 years who smoke cigarettes. Given the patient's fear of surgery and because she is not certain whether she wants to have more children in the future, surgical sterilization via tubal ligation is not a choice. Barrier methods are too much of an inconvenience to the patient's busy lifestyle. A vasectomy might not be welcomed by the boyfriend. Given that both the patient and her boyfriend have no history of STDs and are in a long-term relationship, the best method of contraception

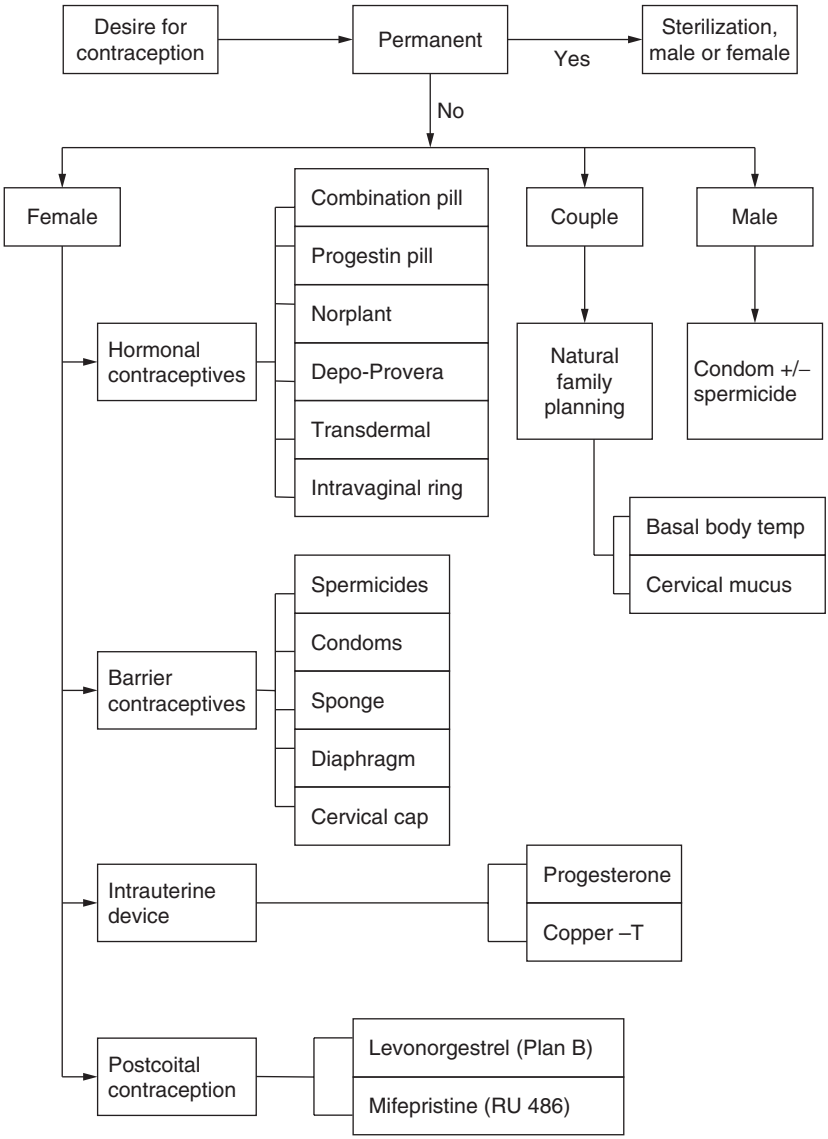

Figure 28–1. Algorithm of family planning options.

for them may be an intrauterine device (IUD). IUDs can last 5 to 10 years before replacement, do not require the woman's busy lifestyle to be inconvenienced, and, in appropriately selected cases, are safe, effective, and well tolerated. Figure 28–1 is an algorithm that can be used as a guide to approaching family planning options.

APPROACH TO Contraception

DEFINITIONS

INTRAUTERINE CONTRACEPTIVE DEVICES (IUD): Small T-shaped device, usually plastic with or without copper or a progestin, placed in the endometrial cavity as a method of long-term contraception.

TYPICAL USE EFFECTIVENESS: Overall efficacy in actual use, when forgetfulness and improper use occur.

PERFECT USE EFFECTIVENESS: Efficacy of a method when always used correctly, consistent and reliable use occur.

BARRIER CONTRACEPTIVE: Prevents sperm from entering upper female reproductive tract.

STEROID HORMONE CONTRACEPTION: Synthetic estrogen and/or progestin to provide contraception in various methods, including oral contraceptive pills, contraceptive patch, contraceptive ring, contraceptive injection, and implant.

CLINICAL APPROACH

The decision process regarding which contraception agent to use in which patient is complex. Review of the patient's individual situation, medical problems, ability to remember to take medication each day plays a role. Table 28–1 summarizes some of the characteristics of various contraceptive agents.

HORMONAL CONTRACEPTION

Hormonal contraception involves ways of delivering estrogen and progesterone. Hormones interact with the body and have the potential for serious side effects, although this is rare. When properly used, hormonal methods are extremely effective. Hormonal methods are available only by prescription.

Oral Contraceptives

There are **two types of oral contraceptive pills (OCPs):** combination pills, which contain both estrogen and a progestin (a natural or synthetic progesterone), and "minipills," which contain only progestin. The combination pill suppresses ovulation through inhibition of the hypothalamic–pituitary–ovarian axis, alters the cervical mucus, retards sperm entry, and discourages implantation into an unfavorable endometrium. **Combination oral contraceptives offer significant protection against ovarian cancer, endometrial cancer, iron-deficiency**

Table 28–1 CONTRACEPTION AGENTS COMPARED INCLUDING BEST-SUITED PATIENTS

CATEGORY/ AGENTS	MECHANISM	BEST SUITED FOR	DISADVANTAGES AND CONTRAINDICATIONS
Barrier • Diaphragm • Cervical caps • Condoms (male and female)	Mechanical obstruction	Not desiring hormones **Decrease STI**	Pelvic organ prolapse Patient discomfort with placing devices on genitals **Lack of spontaneity** Allergies to material Diaphragm may be associated with more UTIs
Combined hormonal (estrogen and progestin) • Combined oral contraceptives • Contraception patch • Vaginal ring	Inhibit ovulation Thickens cervical mucous to inhibit sperm penetration Alters motility of uterus and fallopian tubes Thins the endometrium	Iron deficiency anemia Dysmenorrhea Ovarian cysts Endometriosis **OCP—take pill each day** **PATCH—less to remember but ? more nausea** **RING–less to remember, ?vaginal irritation, and discharge**	Known thrombogenic mutations Prior thromboembolic event Cerebrovascular or coronary artery disease (current or remote) Cigarette smoking over the age of 35 Uncontrolled hypertension Diabetic retinopathy, nephropathy, peripheral vascular disease Known or suspected breast or endometrial cancer Undiagnosed vaginal bleeding Migraines with aura Benign or malignant liver tumors, active liver disease, liver failure Known or suspected pregnancy

(*Continued*)

Table 28–1 CONTRACEPTION AGENTS COMPARED INCLUDING BEST-SUITED PATIENTS (CONTINUED)

CATEGORY/ AGENTS	MECHANISM	BEST SUITED FOR	DISADVANTAGES AND CONTRAINDICATIONS
Progestin-only oral • Minipill	Thickens cervical mucous to inhibit sperm penetration Alters motility of uterus and fallopian tubes Thins the endometrium	**Breast-feeding**	Very dependent on taking pill each day at same time Patient needs to remember to take pill
Injectables • Depo-medroxy progesterone acetate	Inhibits ovulation Thins endometrium Alters cervical mucous to inhibit sperm penetration	Breast-feeding Desires long-term contraception Iron deficiency anemia **Sickle cell disease** **Epilepsy** Dysmenorrhea Ovarian cysts Endometriosis	Depression ? Osteopenia/ osteoporosis Weight gain
Implants (subdermal in arm) • Levonorgestrel • Implant (Implanon)	Inhibits ovulation Thins endometrium Thickens cervical mucous to inhibit sperm penetration	Breast-feeding Desires long-term contraception (lasts for 3 years) Iron deficiency anemia Dysmenorrhea Ovarian cysts Endometriosis	Current or past history of thrombosis or thromboembolic disorders Hepatic tumors (benign or malignant), active liver disease Undiagnosed abnormal vaginal bleeding Known or suspected carcinoma of the breast or personal history of breast cancer Hypersensitivity to any of the components of Implanon **May lead to irregular vaginal bleeding**

Table 28–1 CONTRACEPTION AGENTS COMPARED INCLUDING BEST-SUITED PATIENTS (CONTINUED)

CATEGORY/ AGENTS	MECHANISM	BEST SUITED FOR	DISADVANTAGES AND CONTRAINDICATIONS
IUD • Levonorgestrel IUS	Thickens cervical mucous Thins endometrium	Desires long-term, reversible contraception Stable, mutually monogamous relationship Menorrhagia Dysmenorrhea (NOTE: decreased bleeding and dysmenorrhea)	**Current STI or recent PID** Unexplained vaginal bleeding Malignant gestational trophoblastic disease Untreated cervical or endometrial cancer Current breast cancer Anatomical abnormalities distorting the uterine cavity Uterine fibroids distorting endometrial cavity
• Copper-T	Inhibits sperm migration and viability Changes transport speed of ovum Damages ovum	Desires long-term, reversible contraception (10 years) Stable, mutually monogamous relationship Contraindication to contraceptive steroids	Current STI Current or PID within the past 2 months Unexplained vaginal bleeding Malignant gestational trophoblastic disease Untreated cervical or endometrial cancer Current breast cancer Anatomical abnormalities distorting the uterine cavity Uterine fibroids distorting endometrial cavity **Wilson disease** **May cause more bleeding or dysmenorrhea**
Permanent sterilization • Bilateral tubal occlusion	Mechanical obstruction of tubes	Does not desire more children	Contraindications to surgery May want children in the future

anemia, pelvic inflammatory disease (PID), and fibrocystic breast disease. Women who take combination pills have a lower risk of functional ovarian cysts. The minipill reduces cervical mucus and causes it to thicken. The mucus thickening prevents the sperm from reaching the egg and keeps the uterine lining from thickening, which prevents the fertilized egg from implanting in the uterus. When taken as directed, the failure rate for the minipill is 1% to 3%; the failure rate of the combination pill is 1% to 2%.

Women over the age of 35 who smoke cigarettes and women with certain medical conditions should not take the OCP. Table 28–2 lists the absolute and relative contraindications to taking the OCP. Minor side effects, which usually subside after a few months of usage, include nausea, headaches, breast swelling, fluid retention, weight gain, irregular bleeding, and depression.

When starting an OCP, patients should take the first pill the first day after the start of menses. Many women choose to start on the Sunday after the start of their menses for convenience. Postpartum, non–breast-feeding women should start the OCP during the fourth week after delivery. OCPs can be started the day after an induced or spontaneous abortion. **If a pill is missed, it should be taken as soon as possible and the next dose should be taken as usual.** If two pills are missed, take two pills together on 2 consecutive days to catch up and alternative contraception should be used for 7 days.

The effectiveness of OCPs may be reduced by a few other medications, including some antibiotics, barbiturates, and antifungal medications. On the other hand, OCPs may prolong the effects of theophylline, benzodiazepine, and caffeine.

Table 28–2 CONTRAINDICATIONS TO HORMONAL CONTRACEPTION

ABSOLUTE CONTRAINDICATIONS	RELATIVE CONTRAINDICATIONS
Thrombophlebitis, thromboembolic disease	Severe vascular headache (migraine, cluster)
Cerebral vascular disease	Severe hypertension (if younger than 35-40 years of age and in good medical control, can elect OCP)
Coronary occlusion	Diabetes mellitus (prevention of pregnancy outweighs the risk of complicating vascular disease diabetic who is younger than in age 35-40 years)
Impaired liver function	Gallbladder disease (may exacerbate emergence of symptoms when gallstones are present)
Known or suspected breast cancer	Obstructive jaundice in pregnancy
Undiagnosed abnormal vaginal bleeding	Epilepsy (antiepileptic drugs may decrease effectiveness of OCPs)
Known or suspected pregnancy	Morbid obesity
Smokers older than the age of 35 years	
Congenital hyperlipidemia	

Medroxyprogesterone (Depo-Provera)

Medroxyprogesterone (Depo-Provera) is an injectable form of a progestin. Depo-Provera has a failure rate of only 1%. **Each injection provides contraceptive protection for 14 weeks.** It is injected every 3 months into a muscle in the buttocks or arm. Its side effects include irregular menses, weight gain, and facial/body hair growth. In addition, there may be irregular bleeding and spotting during the first months followed by periods of amenorrhea. About half of women develop amenorrhea after a year of Depo-Provera use. There may be a prolonged period of time prior to return of fertility after discontinuing Depo-Provera.

Transdermal Contraceptive

A transdermal contraceptive patch (Ortho Evra) is available. It is a combined hormone patch containing norelgestromin (the active metabolite of norgestimate) and ethinyl estradiol. The treatment regimen for each cycle is three consecutive 7-day patches followed by one patch-free week, so that withdrawal bleeding can occur. **The patch's efficacy and side effects are comparable to that of combined OCPs,** although there may be an increased risk of vascular thrombosis with use of the patch.

Intravaginal Ring Contraceptive

NuvaRing is a flexible, transparent ring made of ethylene vinyl acetate copolymers that delivers etonogestrel and ethinyl estradiol. **A woman inserts the NuvaRing herself, wears it for 3 weeks, then removes and discards the device.** After one ring-free week, during which withdrawal bleeding occurs, a new ring is inserted. The side effects of NuvaRing are similar to those of combined OCPs, with the main adverse effect being disrupted bleeding.

Spermicides Used Alone

Spermicides come in many forms (foams, jellies, gels, and suppositories) and work by forming a physical and chemical barrier to sperm. They should be inserted into the vagina within an hour before intercourse. If intercourse is repeated, more spermicide should be inserted. The active ingredient in most spermicides is the chemical nonoxynol-9. The failure rate for spermicides in preventing pregnancy when used alone is 20% to 30%. Spermicides are available without a prescription. When **spermicides are used with a condom, the failure rate is comparable to that of oral contraceptives** and is much better than for either spermicides or condoms used alone.

BARRIER METHODS

There are **five barrier methods of contraception:** male condoms, female condoms, diaphragm, sponge, and cervical cap. In each, the method works by

keeping the sperm and egg apart. The main possible side effect is an allergic reaction either to the material of the barrier or the spermicides that should be used with them. Using the methods correctly for each and every sexual intercourse gives the best protection.

Male Condom

Condoms on the market are made of either latex rubber or natural skin (from sheep intestines). Of these two types, **only latex condoms are highly effective in preventing STDs.** Latex provides a good barrier to viruses such as HIV and hepatitis B. Each condom can only be used once. Condoms have a birth control failure rate of approximately 15%, with most of the failures a result of improper use. Some condoms have spermicide added, which may give some additional contraceptive protection. Vaginal spermicides may also be added before sexual intercourse.

Female Condom

The Reality Female Condom consists of a lubricated polyurethane sheath with a flexible polyurethane ring on each end. One ring is inserted into the vagina much like a diaphragm, while the other remains outside, partially covering the labia. The female condom may offer some protection against STDs; however, for highly effective protection, male latex condoms must be used. The estimated yearly failure rate ranges from 21% to 26%.

Sponge

The contraceptive sponge is made of white polyurethane foam. The sponge, shaped like a small doughnut, contains the spermicide nonoxynol-9. It is inserted into the vagina to cover the cervix during and after intercourse. It does not require fitting by a health professional and is available without prescription. It is to be used only once and then discarded. The failure rate is between 18% and 28%. An extremely rare side effect is toxic shock syndrome (TSS).

Diaphragm

The diaphragm is a flexible rubber disk with a rigid rim ranging in size from 2 to 4 in. in diameter. It is designed to cover the cervix during and after intercourse, so that sperm cannot reach the uterus. Spermicidal jelly or cream must be placed inside the diaphragm for it to be effective. The diaphragm must be fitted by a health professional and the correct size prescribed to ensure a snug seal with the vaginal wall. If intercourse is repeated, additional spermicide should be added with the diaphragm still in place. The **diaphragm should be left in place for at least 6 hours after intercourse.** The diaphragm used with spermicide has a failure rate of from 6% to 18%.

Cervical Cap

The cervical cap is a dome-shaped rubber cap in various sizes that fits snugly over the cervix. Like the diaphragm, it is used with a spermicide and must be fitted by a health professional. It is more difficult to insert than the diaphragm, but may be left in place for up to 48 hours. There also appears to be an increased incidence of irregular Papanicolaou (Pap) tests in the first 6 months of using the cap, and TSS is an extremely rare side effect. The cap has a failure rate of about 18%.

INTRAUTERINE DEVICES

IUDs are small, plastic, flexible devices that are inserted into the uterus through the cervix by a trained physician. **Only two IUDs are presently marketed in the United States:** ParaGard T380A, a T-shaped device partially covered by copper and effective for 10 years, and Mirena, which is also T-shaped but contains a progestin released over a 5-year period. The copper-T IUD has a 4% to 5% failure rate while the Mirena has a failure rate of less than 1%. An IUD alters the uterine and tubal fluids, particularly in the case of copper-bearing IUDs, inhibiting the transport of sperm through the cervical mucus and uterus. Progesterone-containing IUDs also thin the uterine lining. The risk of PID with IUD use is highest in those women with multiple sex partners or who have a history of previous PID. Consequently, the **IUD is recommended primarily for women in mutually monogamous relationships.**

Absolute contraindications for IUD include current, recent (within 3 months), or recurrent endometritis, PID, or STD; pregnancy; anatomically distorted uterine cavity; and known or suspected HIV infection. Relative contraindications include any history of gonorrhea or *Chlamydia*; multiple sexual partners or a partner with multiple other partners; undiagnosed abnormal vaginal bleeding; known or suspected uterine or cervical malignancy; and previous problems with an IUD (pregnancy, expulsion, perforation, pain, heavy bleeding). In addition to PID, other complications include perforation of the uterus, septic abortion, and ectopic pregnancy. Women may also experience some short-term side effects such as cramping and dizziness at the time of insertion; bleeding, cramps, and backache that may continue for a few days after the insertion; spotting between periods; and longer and heavier menstruation during the first few periods after insertion. The patient should check that the string is palpable each month after her menses. Between 2% and 10% of women expel their IUD within the first year. The absolute rate of ectopic pregnancy is reduced with the IUD because of its high contraceptive efficacy. However, when accidental pregnancy does occur, there is an increased proportion of ectopic pregnancy. Adolescence and nulliparity are not contraindications in properly selected young women in monogamous relationships.

NATURAL FAMILY PLANNING

Periodic abstinence (natural family planning or rhythm method) entails not having sexual intercourse during the woman's fertile period. Using periodic abstinence is dependent on the ability to identify the approximately 10 days in each menstrual cycle that a woman is fertile. Periodic abstinence has a failure rate of 14% to 47%. Women with irregular cycles have the highest failure rates. The basal body temperature method is based on the knowledge that just before ovulation a woman's basal body temperature drops several tenths of a degree and after ovulation it returns to normal. The method requires that the woman take her temperature each morning before she gets out of bed. There are now electronic thermometers with memories and electrical resistance meters that can more accurately pinpoint a woman's fertile period. The cervical mucus method, also called the Billings method, depends on a woman recognizing the changes in cervical mucus that indicate ovulation is occurring or has occurred.

SURGICAL STERILIZATION

Tubal ligation seals a woman's fallopian tubes so that an egg cannot travel to the uterus. Vasectomy involves closing off a man's vas deferens so that sperm will not be carried to the penis. Vasectomy is a minor surgical procedure, most often performed in a doctor's office under local anesthesia. Tubal ligation is an operating room procedure performed under general anesthesia. Major complications, which are rare in female sterilization, include infection, hemorrhage, and problems associated with the use of general anesthesia. The failure rate is less than 1%. Although there has been some success in reopening the fallopian tubes and the vas deferens, the success rate is low, and **sterilization should be considered irreversible.**

EMERGENCY CONTRACEPTION

All female patients of reproductive age should be made aware of postcoital contraception. This knowledge does not increase the likelihood of high-risk behavior. The **Yuzpe method consists of taking combined OCPs for emergency contraception.** High doses of oral contraceptives, begun within 72 hours of unprotected intercourse, decrease the risk of pregnancy by 74%. Only RU-486 (mifepristone) is effective after 72 hours. Consider prescribing an antiemetic, as nausea and vomiting are common side effects. Two oral doses of levonorgestrel (Plan B) 0.75 mg, with 12 hours between doses, is an effective and well-tolerated regimen. Preven, a convenient emergency contraception kit, includes two doses of medication and a pregnancy test. Mifepristone (RU-486) 600 mg in a single dose is the most effective emergency contraceptive and has the fewest side effects.

LEVONORGESTREL IMPLANTS

Levonorgestrel in Silastic capsules (Norplant) was the first contraceptive implant. In a minor surgical procedure, six matchstick-size rubber capsules containing progestin were placed just underneath the skin of the upper arm. The implant was effective within 24 hours and provided progestin for up to 5 years. The failure rate for Norplant was less than 1% for women who weighed less than 150 lb. The potential side effects of the implant included irregular menstrual bleeding, headaches, nervousness, depression, nausea, dizziness, skin rash, acne, change of appetite, breast tenderness, weight gain, enlargement of the ovaries or fallopian tubes, and excessive growth of body and facial hair. Norplant is no longer manufactured.

Comprehension Questions

28.1 While working in the clinic of the county jail you see a G6P2032 for a well woman's examination. She openly tells you that she was arrested for a history of prostitution. On arrest she was found to be HIV positive. She is to be released next week and would like to have an IUD placed. Which of the following agents is contraindicated in this patient?

A. Oral contraceptive agent
B. Depot medroxyprogesterone
C. Intrauterine contraceptive device
D. Condoms
E. Cervical cap

28.2 An 18-year-old woman reported having intercourse with her boyfriend 20 hours ago. She was concerned because the condom broke. She used no other form of contraception and did not elect to use "emergency contraception." The patient reported a history of regular periods since age 14 of moderate flow that lasts for 4 days at a time. She is 5'8" and 165 lb. She plays as a forward on her high school basketball team and is worried about becoming pregnant. What is her risk of pregnancy?

A. Greater than 40%
B. Approximately 30%
C. Approximately 15%
D. Approximately 8%
E. Less than 1%

28.3 A 32-year-old woman reports that she and her acquaintance had consensual intercourse 2 days ago but the condom broke. They used no other form of contraception and she has not taken oral contraceptives since she was in college. She is midcycle in a regular 28-day cycle. She has had chlamydial cervicitis in the past and was treated with antibiotics. She currently takes tetracycline for mild to moderate acne. Her pregnancy test is negative but she still desires something to prevent pregnancy. Which of the following is the most appropriate method of "emergency contraception"?

A. Yuzpe method
B. Plan B method
C. Insertion of an IUD
D. Intramuscular methotrexate

28.4 A 36-year-old woman is seeking contraception. She has delivered her baby 8 weeks ago and is breast feeding. She undergoes a history and physical examination, and is counseled regarding the various options. She is healthy, drinks an occasional glass of wine per month, and smokes half a pack of cigarettes per day. Her blood pressure is 140/98 mm Hg. The patient prefers the combination oral contraceptive agent. However, her physician notes some findings that represent risks for taking the oral conceptive. Which of the following is the most important contraindication to OCPs in this patient?

A. History of hepatitis B infection
B. Family history of thromboembolism
C. Patient breast-feeding
D. Hypertension
E. Smoking status

ANSWERS

28.1 **C.** Known or suspected HIV infection is a contraindication to IUD placement. IUDs can be used in selected nulliparous women and in women who desire future fertility. A history of an STD is a relative, but not an absolute, contraindication to IUD use. This patient has a high likelihood of sexually transmitted infections, and thus, IUD is contraindicated. Oral contraceptives and depot medroxyprogesterone decreases the risk of PID by thickening the cervical mucus. Condom use also decreases the risk of STI.

28.2 **D.** Approximately 8% of women will become pregnant after a single act of coitus.

28.3 **B.** Emergency contraception may include combination hormonal therapy at time zero and at 72 hours; many OCPs are effective if used in the right doses and within 72 hours. Plan B is levonorgestrel and is more effective than the combined OCPs for postcoital contraception. In addition, it does not have the prominent side effect of nausea. The IUD is relatively contraindicated in this patient because of her history of *Chlamydia* infection.

28.4 **E.** Smoking over the age of 35 years is an absolute contraindication to the combination OCP due to an increased risk of DVT, MI, and stroke. A family history of thromboembolism is not a contraindication to OCP use as is a personal history. Hypertension with a BP greater than 160/100 is another contraindication, whereas mildly elevated blood pressure is not a contraindication; nevertheless the blood pressure should be monitored. All women should be advised to quit smoking.

Clinical Pearls

- The male latex condom remains the best shield against AIDS and other STDs.
- Barrier methods, which work by keeping the sperm and egg apart, usually have only minor side effects.
- Combination oral contraceptives offer significant protection against ovarian cancer, endometrial cancer, iron-deficiency anemia, PID, and fibrocystic breast disease.
- Methods of hormonal contraception, when used properly, are extremely effective.
- Surgical sterilization must be considered permanent. Vasectomy is considered safer than tubal ligation.
- Noncontraceptive benefits of combination oral contraceptives include decreased incidence of benign breast disease, relief from menstrual disorders (dysmenorrhea and menorrhagia), reduced risk of uterine leiomyomata, protection against ovarian cysts, reduction of acne, improvement of bone mineral density, and a reduced risk of colorectal cancer.

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Case 29

A 16-year-old adolescent female presents for a routine well examination. She is a junior in high school and has no significant medical history. She plays on the school softball team and has a preparticipation clearance form for you to complete. She is accompanied by her mother who wants to know if her daughter should start having routine gynecologic examinations as part of her routine checkup. She states that the patient's last tetanus shot was at the age of 5 years. She received all of the routine childhood immunizations, including a complete hepatitis B series, and had chickenpox when she was 6 years old. The mother reports that there are no medical problems in the immediate family, but that one of the patient's cousins died at the age of 21 years of a sudden cardiac death. When interviewed without the mother in the room, the patient reports to you that she is generally happy, she gets As and Bs in school, and has an active social life. She denies ever being involved in sexual activity, or tobacco or drug use. She says that she will have a "drink or two" at a party with her friends. On examination, her vital signs are normal. Examination of her head and neck, lungs, abdomen, skin, and musculoskeletal and nervous systems are normal. On cardiac auscultation, you hear a 2/6 systolic murmur that gets louder when you have her Valsalva. Peripheral pulses are strong and symmetric; there is good capillary refill and no sign of cyanosis.

- What immunizations should be recommended at this visit?
- At what age is it recommended to start routine Papanicolaou (Pap) smear screening?
- What is the most common cause of sudden cardiac death in young athletes?

ANSWERS TO CASE 29:
Adolescent Health Maintenance

Summary: A healthy 16-year-old adolescent female presents for a routine checkup and sports preparticipation examination. She is noted incidentally to have a heart murmur.

- **Recommended immunization:** Tetanus-diphtheria-acellular pertussis (Tdap) booster and meningococcal vaccination; consideration can be given to starting the human papilloma virus (HPV) vaccine series as well.
- **Recommended age to start routine Pap smears:** Within 3 years of the start of sexual activity or age 21, whichever comes first.
- **Most common cause of sudden cardiac death in young athletes:** Hypertrophic cardiomyopathy (HCM).

ANALYSIS

Objectives

1. Be familiar with the recommendations of the Guidelines for Adolescent Preventive Services (GAPS) for screening examinations and counseling in adolescents.
2. Know the immunizations routinely recommended for adolescents and teenagers.
3. Know the components of and the rationale for performing sports preparticipation examinations

Considerations

This is a healthy adolescent female who comes in for a sports preparticipation physical examination. This is also an opportunity for other health maintenance such as immunizations, screening for eating disorders, and education. Her history is unremarkable, and she has a 2/6 systolic murmur which increases with Valsalva. The history is the most important component to the sports physical examination. The focus should be on conditions that can lead to sudden cardiac death, which are usually cardiovascular, most commonly hypertrophic cardiomyopathy. Marfan syndrome is associated with aortic root dilation or dissection, hence stigmata of Marfan and family history is also important. The hallmark physical examination finding in HCM is a systolic murmur that decreases in intensity with the athlete in the supine position (increased ventricular filling, decreased obstruction). This contrasts with functional outflow murmurs common in athletes that *increase* in intensity upon lying down. The intensity

of the HCM murmur increases with the Valsalva maneuver (decreased ventricular filling, increased obstruction). Any athlete who has a systolic murmur with an intensity of 3/6 or greater; a diastolic, holosystolic, or continuous murmur; or any other murmur that the examiner finds suspicious should be held from participation and referred to a cardiologist for evaluation. Most athletes with HCM are, however, asymptomatic. The individual in this case has only a grade 2/6 murmur, but it is worrisome that it increases in intensity with Valsalva. Most murmurs will decrease in intensity and duration with Valsalva. For this reason, this patient may benefit from referral to cardiology.

APPROACH TO Adolescent Health

DEFINITIONS

GUIDELINES FOR ADOLESCENT PREVENTIVE SERVICES (GAPS): A series of recommendations regarding the delivery of health services, promotion of well-being, screening for common conditions, and provision of immunizations for adolescents and young adults between the ages of 11 and 21 years.

HPV VACCINE: An immunization against four high-risk strains of human papillomavirus is available and recommended for adolescent girls and young women, HPV subtypes 6 and 11 (prevent venereal warts) and 16 and 18 (prevent a large fraction of cervical dysplasia/cancer). It is a series of three injections over 6 months that has been shown to be efficacious at reducing the incidence of genital warts and cervical cancer associated with the particular strains of HPV that are included in the vaccine.

CLINICAL APPROACH

Adolescence is a time of physical, emotional, and psychosocial changes. It is also a time of experimentation and, frequently, risk taking. Fortunately, adolescence is also a time of relatively good health for most. However, the choices made during adolescence can affect both the short-and long-term health of the patient. Addressing the unique healthcare needs of adolescents can be difficult, as they may be more likely to present to the physician for acute illness than for health maintenance. For this reason, physicians should take the opportunity to consider age-appropriate health maintenance at each encounter with an adolescent and young adult.

Numerous issues can serve as barriers to providing effective care to adolescent patients; one of these is confidentiality. Many adolescents believe that

physicians share any information provided with the parent. Consequently, they may not volunteer information, such as sexual activity or use of tobacco, alcohol, and drugs. One commonly used technique to address this is to take a history with the parent in the room, to allow the parent to present any concerns, then interview the patient alone, to allow the patient to speak confidentially with the doctor. **Physicians who treat adolescent patients should have policies in place to ensure doctor–patient confidentiality while balancing the parent's right to be involved with the child's care.** These policies should be discussed with and agreed to by the patient and parent in advance, so as to promote an honest, trusting, and therapeutic relationship.

The American Medical Association has published ***Guidelines for Adolescent Preventive Services (GAPS),*** a series of recommendations regarding the delivery of health services, promotion of well-being, screening for common conditions, and provision of immunizations for adolescents and young adults between the ages of 11 and 21 years. These services are intended to be delivered as part of a series of annual health-care visits that address biomedical and psychosocial aspects of health and emphasize preventive services. These visits should include at least three complete physical examinations, one in early adolescence (age 11–14), one in middle adolescence (age 15–17), and one in late adolescence (age 18–21).

The **GAPS recommend counseling for both parents and adolescents.** It recommends that physicians provide guidance to parents on normal physical, sexual, and emotional development, signs of physical and emotional problems, parenting behaviors to promote health, and methods to help their child avoid harmful behaviors. The adolescent patient should receive counseling annually on their growth and development, injury prevention, healthy diet, exercise, and avoidance of harmful substances (alcohol, tobacco, drugs, anabolic steroids). Guidance should also emphasize responsible sexual behaviors, including abstinence and contraception, to reduce the risks of sexually transmitted diseases (STDs) and pregnancy.

GAPS recommend the routine screening for several medical, behavioral, and emotional conditions. All adolescents should be screened annually for hypertension, with further evaluation and treatment for those whose blood pressure is above the 90th percentile for their gender and age. All should be screened annually for eating disorders and obesity. All should also be screened for the use of tobacco (both cigarettes and smokeless tobacco), alcohol, and other abusable substances. Routine toxicology screening, however, is not recommended. Lipid screening is recommended for those at above-average risk based on a personal history of comorbid conditions or a family history of hyperlipidemia, coronary artery disease, or other vascular diseases. Tuberculosis (TB) skin testing should be performed in those at high risk. These risks include having lived (or living) in a homeless shelter or in an area with a high prevalence of TB, having been (or being) incarcerated, having been exposed to active TB, and working in a health-care setting.

All adolescents should be asked about sexual behaviors, including sexual orientation, use of contraception, number of sexual partners, and history of pregnancy or STDs. **Sexually active females should be screened for gonorrhea and *Chlamydia* by cervical sampling.** Cervical cancer screening should also be performed in sexually active females. The United States Preventive Services Task Force (USPSTF), in a 2003 guideline, states that screening for cervical cancer with Pap smears should begin within 3 years of onset of sexual activity or age 21 years, whichever comes first. **Sexually active males can be screened for presumptive gonorrhea and *Chlamydia* infections by urine test for leukocyte esterase.** Males and females at risk for HIV should be offered confidential testing.

Other recommendations include screening all adolescents annually for depression and risk of suicide, with appropriate management or referral of those in need. All should also be questioned annually about emotional, physical, or sexual abuse. Every state mandates the reporting of suspected abuse of minors to the designated child welfare agency or child protective service. Difficulties at school or with learning should also be evaluated annually, with subsequent management to be coordinated with the school and parent/guardian.

The adolescent health visit is also a time to ensure that the patient is appropriately immunized against preventable infections. In those who have received the recommended primary series, a tetanus-diphtheria (Td) booster is recommended at ages 11 to 12 years and then every 10 years thereafter. Because of the continued risk for infection with pertussis, a Tdap is recommended in place of one Td booster for adolescents and adults. Varicella vaccine should be offered to those who have not been vaccinated and who do not have a history of chickenpox. A measles-mumps-rubella (MMR) booster should be given if the patient did not receive a booster at ages 4 to 6 years. The hepatitis B series should be given to any adolescent who has not been previously immunized. Hepatitis A vaccine can be offered to those who live in areas with high infection rates, travel to high-risk areas, have chronic liver disease, or inject IV drugs, and to males who have sex with males.

In 2005, the Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices added a new recommendation for routine meningococcal vaccination using a tetravalent polysaccharide-protein conjugate vaccine (MCV4). Routine vaccination is recommended at ages 11 to 12 years. If not previously vaccinated, vaccination before high school is advised. Vaccination is also recommended for college freshmen living in dormitories and for others at increased risk, such as military recruits, travelers to endemic areas, or the functionally/anatomically asplenic.

A vaccination against four high-risk strains of human papillomavirus is available and recommended for adolescent girls and young women. It is a series of three injections over 6 months that has been shown to be efficacious at reducing the incidence of genital warts and cervical cancer associated with the particular strains of HPV that are included in the vaccine. It is preferred

to provide this vaccination prior to the onset of sexual activity, so the series can be started in girls as young as 9 years old, but it is routinely recommended for the ages of 11 to 12. It is also recommended for females aged 13 to 26 who have not completed the vaccine series. The HPV vaccine is also useful for those who have started sexual activity, as it may protect against strains of HPV to which the patient has not been exposed.

SPORTS PREPARTICIPATION EXAMINATION

A common reason for healthy adolescents to present to primary care physicians is for a preparticipation examination as a requirement to play a sport in school. The goal of these examinations is to attempt to identify conditions that may place a young athlete at risk during athletic participation. These conditions are primarily cardiac and orthopedic, but are not limited to these systems. **A preparticipation examination allows the physician to provide the comprehensive health maintenance, including counseling, anticipatory guidance, screening, and vaccination, recommended in the GAPS guidelines.** These encounters also serve to meet legal and insurance requirements of the school or school system.

The rate of sudden cardiac death in athletes is very low. Congenital cardiac anomalies are the most common etiology, with hypertrophic cardiomyopathy accounting for about one-third and anomalous coronary arteries for about one-fifth of cardiac anomalies. The **history is the most important tool in screening for these abnormalities.** All adolescents and their parents should be asked about personal history of exertional chest pain, dyspnea, syncope, history of heart murmurs, and family history of hypertrophic cardiomyopathy, other congenital cardiac abnormalities, or premature cardiac deaths. Other important historical information includes history of asthma or other pulmonary disorders, orthopedic injuries, heat-related illness, and absence of one of a paired organ (eg, single kidney, testicle, ovary, etc).

It is important to screen for eating disorders, as well as for a desire to change body weight, either for body image or for athletic purposes (eg, "weight cutting" for wrestlers). Eating disorders are more common in female than male athletes. Females should be questioned about menstrual irregularities, as amenorrhea could signal anorexia and amenorrheic female athletes could be at risk for osteoporosis.

The examination should be thorough, but several aspects should be emphasized. Blood pressure should be measured and compared with age-and gender-appropriate norms. General appearance, specifically looking for signs of Marfan syndrome, should be noted. These signs, which include arachnodactyly, an arm span greater than height, pectus excavatum, tall-thin habitus, high-arched palate, and ocular lens subluxations, should prompt further evaluation, as persons with Marfan can have aortic abnormalities that predispose to rupture during sports. Auscultation of the heart should be performed, at minimum, in both

the lying and standing positions. **The murmur of hypertrophic cardiomyopathy, while not always present, is best heard along the left sternal border and accentuates with activities that decrease cardiac preload and end diastolic volume of the left ventricle.** Therefore, standing or straining with a Valsalva maneuver would increase the murmur; conversely, squatting would be expected to decrease the murmur. **Any adolescent with stigmata of Marfan syndrome, a murmur suggestive of hypertrophic cardiomyopathy, with a grade 3/6 or louder systolic murmur, or any diastolic murmur should be evaluated by a cardiologist prior to clearance for athletic participation.**

No specific tests are recommended for universal screening of all athletes, although specific tests may be indicated based upon history or physical examination findings. Echocardiography is the study of choice for the diagnosis of hypertrophic cardiomyopathy.

Participation in athletics or exercise should be encouraged. **Absolute contraindications to all athletic participation are rare;** more commonly, clearance to participate may be delayed for further evaluation of a suspected condition, rehabilitation of an injury, or recovery from an acute illness. In almost all cases, an adolescent should be able to find some athletic pursuit in which the he/she may participate.

Comprehension Questions

29.1 A high school student is being seen for a sports preparticipation examination. Which of the following should prompt a referral to a cardiologist prior to clearance to participate in high school sports?

A. Grade 2/6 systolic murmur in an asymptomatic 16-year-old adolescent female
B. Grade 1/6 diastolic murmur heard at the apex in a 17-year-old adolescent female
C. Grade 2/6 systolic murmur in a 17-year-old adolescent male that is heard while lying down and that gets softer when standing
D. An asymptomatic 16-year-old whose grandfather died of a heart attack at age 72

29.2 A 15-year-old girl is brought in by her mother for a wellness clearance for sports participation at school. She would also like to discuss the addition of birth control. When the mother leaves the room you learn that the girl is not sexually active but wants to start OCPs because she has heard they help with acne and her friends have seen improvement. She does not drink alcohol or smoke and is in honors classes in the ninth grade. She plays on the junior varsity softball team and eats most days in the school cafeteria. Which of the following is recommended routinely in the Guidelines for Adolescent Preventive Services and should be performed at this time?

A. Annual complete physical examinations between the ages of 11 and 21 years
B. Periodic screening for drug use with a urine toxicology test
C. Cholesterol testing
D. Annual screening for hypertension

29.3 A 17-year-old adolescent male reports that he has been sexually active with two female partners in the past year. He has used condoms "sometimes, but not always." He is asymptomatic and has a normal physical examination. Which of the following tests would be recommended to screen him for gonorrhea and *Chlamydia*?

A. Urethral swab
B. Serum antibodies to *Neisseria gonorrhoeae* and *Chlamydia trachomatis*
C. Urine for leukocyte esterase
D. No screening is recommended

ANSWERS

29.1 **B.** Any patient with a diastolic murmur, grade 3/6 or louder systolic murmur, murmur suggestive of hypertrophic cardiomyopathy, or signs of Marfan syndrome should be evaluated by a cardiologist prior to clearance to participate in athletics. The murmur of hypertrophic cardiomyopathy typically gets louder with maneuvers that reduce preload, such as the Valsalva maneuver or when standing.

29.2 **D.** GAPS recommend annual screening for hypertension by blood pressure measurement in all adolescents. Complete physical examinations are advised routinely, once during early adolescence, once in midadolescence, and once in late adolescence, as well as more often when indicated. Lipid screening should be targeted to those who are at high risk based on personal or family history. Routine toxicology screening is not recommended.

29.3 **C.** Urine for leukocyte esterase is recommended as screening for presumptive gonorrhea or *Chlamydia* in sexually active males. A urethral swab is more appropriate for diagnostic testing in a male who has a urethral discharge.

Clinical Pearls

- Adolescents tend to see physicians irregularly. Take the time at each visit, no matter what the chief complaint is, to review health maintenance issues.
- True contraindications to participation in all sports are rare. Almost everyone should be able to participate in some form of athletic activity.
- Universal adolescent vaccination with meningococcal vaccine became a recommendation in 2005; unvaccinated adolescents and teens should be offered vaccination routinely.

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Case 30

A 47-year-old man presents to your office for a follow-up visit. He was seen 3 weeks ago for an upper respiratory infection and noted incidentally to have a blood pressure of 164/98 mm Hg. He vaguely remembered being told in the past that his blood pressure was "borderline." He feels fine, has no complaints, and his review of systems is entirely negative. He does not smoke cigarettes, drinks "a couple of beers on the weekends," and does not exercise regularly. He has a sedentary job. His father died of a stroke at the age of 69 years. His mother is alive and in good health at the age of 72 years. He has two siblings and is not aware of any chronic medical issues that they have. In the office today, his blood pressure is 156/96 mm Hg in his left arm and 152/98 mm Hg in the right arm. He is afebrile, his pulse is 78 bpm, respiratory rate 14 breaths per minute, he is 70 in tall, and weighs 210 lb. A general physical examination is normal.

- What diagnosis (or diagnoses) can you make today?
- What further evaluation needs to be performed?
- What nonpharmacologic intervention(s) may be beneficial?
- What is the recommended initial medication management?

ANSWERS TO CASE 30:
Hypertension

Summary: A 47-year-old man is found to have an elevated blood pressure reading when seen for an unrelated problem visit. On follow-up, his blood pressure remains elevated. He is obese and leads a sedentary lifestyle but does not have other high risks based on his personal or family history.

- **Diagnoses:** Stage 1 hypertension and obesity.
- **Necessary further evaluation:** Blood glucose; serum potassium, creatinine, and calcium levels; hematocrit; urinalysis; electrocardiogram (ECG).
- **Nonpharmacologic interventions:** DASH (Dietary Approaches to Stop Hypertension) diet; alcohol limitation to no more than two drinks per day; increased physical activity; weight reduction.
- **Recommended initial medication:** Thiazide diuretic.

ANALYSIS

Objectives

1. Know the diagnostic criteria for hypertension.
2. Learn the recommended initial evaluation of persons found with an elevated blood pressure.
3. Know the medication and lifestyle modifications that can help to control blood pressure.
4. Learn the complications and risks of uncontrolled hypertension.

Considerations

The patient presented here is typical of one seen every day in primary care offices and represents the most common presentation of hypertension. Most hypertensive patients do not have any symptoms of their disease. They are typically seen for another reason and noted to have a high blood pressure reading. Untreated hypertension significantly raises an individual's risk of myocardial infarction, cerebrovascular accidents, and renal failure, among other conditions. **The risk of cardiovascular disease doubles with each increase in blood pressure of 20/10 mm Hg above 115/75 mm Hg.** Because of the high prevalence of the problem, the lack of symptoms and the demonstrated efficacy of treatment in reducing the risk of complications, the United States Preventive Services Task Force recommends screening every adult

patient for hypertension by measuring their blood pressure. The appropriate screening interval is not clearly defined, but most practitioners will check the blood pressure of every adult patient at every office visit.

APPROACH TO Hypertension

DEFINITIONS

JNC 7: The seventh report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. A comprehensive, evidence-based, expert review of the diagnosis, evaluation, and management of hypertension (available at: www.nhlbi.nih.gov/guidelines/hypertension/express.pdf).

PREHYPERTENSION: Blood pressure between 120 and 139 mm Hg systolic and 80 and 89 mm Hg diastolic.

CLINICAL APPROACH

Hypertension is the most common primary diagnosis at physician office visits in the United States each year. **Approximately 50 million Americans have hypertension and approximately 30% are unaware of their problem.** The prevalence is higher in African Americans and in older patients. National Health and Nutritional Examination Surveys (NHANES) data suggest that hypertension is responsible for approximately one-third of heart attacks, one-half of heart failure, and one-fourth of premature deaths. Most patients with end-stage kidney disease are hypertensive. Hypertensive nephrosclerosis is responsible for approximately one-fourth of end-stage kidney disease. **The risk of complications is directly related to the elevation of the blood pressure—the higher the blood pressure, the higher the risk.**

Elevated systolic blood pressure is a greater risk for cardiovascular disease complications than elevated diastolic pressure. Control of systolic blood pressure tends to be more difficult to achieve, and when it is achieved, the diastolic blood pressure usually comes under control as well. The goal of treatment is to get the blood pressure to less than 140/90 mm Hg. For persons with diabetes or kidney disease, the goal is to achieve a blood pressure of less than 130/80 mm Hg.

Diagnosis and Workup

The diagnosis of hypertension relies on accurate measurement of blood pressure. The appropriate technique is to allow the patient to sit quietly in a chair

(not on the examination table) with a supported back and feet on the floor for 5 minutes prior to making the measurement. The blood pressure should be measured at least twice, using a calibrated sphygmomanometer and an appropriately sized cuff for the patient. The blood pressure cuff should encircle at least 80% of the patient's arm; a cuff that is too small can result in a falsely elevated reading.

The diagnosis of hypertension is made based on the average of two properly taken blood pressure measurements at two or more office visits. JNC 7 places blood pressure readings into one of four categories: normal, prehypertension, stage 1 hypertension, and stage 2 hypertension (Table 30–1). The prehypertension category was a new addition in JNC 7, in recognition of the fact that people with blood pressure in this range have twice the risk of progression to overt hypertension as those with normal blood pressure.

When hypertension is diagnosed, an **evaluation consisting of a history, physical examination, and focused diagnostic studies should be performed, with the goals of assessing overall cardiovascular risks, identification of possibly secondary causes of hypertension, and determination of the presence of any end-organ damage.** Historical information should include personal and family medical histories, an assessment of diet and activity levels, and specific questioning regarding tobacco, alcohol, recreational drug, and medication (both prescription and nonprescription) use. Patients should be questioned about cardiovascular, cerebrovascular, and peripheral arterial disease symptoms.

Along with blood pressure, examination should include all other vital signs and a measurement of body mass index. Other specific components of the examination should include a funduscopic examination for signs of retinopathy, auscultation for carotid, femoral, and renal bruits, palpation of peripheral pulses, abdominal palpation for signs of organomegaly or aortic aneurysm, and a complete cardiopulmonary examination.

Initial testing should include measurement of serum potassium, creatinine (with glomerular filtration rate calculation) and calcium, blood glucose, and

Table 30–1 CLASSIFICATION OF BLOOD PRESSURE

CLASSIFICATION	SYSTOLIC BLOOD PRESSURE (MM HG)	DIASTOLIC BLOOD PRESSURE (MM HG)
Normal	<120	and <80
Prehypertension	120-139	or 80-89
Stage 1 hypertension	140-159	or 90-99
Stage 2 hypertension	≥160	or ≥100

hematocrit. A urinalysis should be done to look for proteinuria or cellular components suggestive of renal disease. An ECG should be performed to evaluate for changes consistent with coronary artery disease and to screen for left ventricular hypertrophy (LVH).

Nonpharmacologic Management

Once the diagnosis of hypertension or prehypertension is made, patients should be advised of specific lifestyle modifications that can both reduce their blood pressure and reduce their overall cardiac risk factors. These should include efforts to lose weight if overweight or obese, an increase in physical activity, and reduced consumption of alcohol. Men should consume no more than two alcoholic beverages a day and women no more than one. Any smoker should be counseled to quit.

A high-potassium and high-calcium diet, the **Dietary Approaches to Stop Hypertension (DASH) diet plan, reduces blood pressure in an amount comparable to single-agent drug therapy.** An informational brochure detailing the DASH diet is available from the National Heart, Lung, and Blood Institute at www.nhlbi.nih.gov/health/public/heart/hbp/dash/new_dash.pdf. Combining the various lifestyle modifications provides additive benefits, and these efforts should continue even when the decision is made to start medications.

Pharmacologic Management

Lowering blood pressure reduces the risk of adverse outcomes such as strokes and heart attacks. In the primary treatment of hypertension, thiazide diuretics are the recommended first-line therapy in most settings, because they are well-tolerated, inexpensive, and no other medication has superior outcomes in head-to-head studies. Patients with stage 1 hypertension, who are inadequately controlled with nonpharmacologic interventions alone, should be started on a thiazide diuretic, unless there is a compelling reason to start another class of medication (Table 30–2). Patients with stage 2 hypertension or anyone whose blood pressure is above the recommended goal by less than or equal to 20/10 mm Hg should be started on combination therapy with two medications given either as separate prescriptions or as a fixed-dose combination of medications.

Table 30–2 INDICATIONS FOR STARTING SPECIFIC CLASSES OF ANTIHYPERTENSIVE MEDICATION

INDICATION	CLASS OF MEDICATION
Diabetes mellitus	Angiotensin-converting enzyme inhibitor Angiotensin receptor blocker Diuretic Calcium channel blocker β-Blocker
High risk of coronary artery disease	Angiotensin-converting enzyme inhibitor β-Blocker Diuretic Calcium channel blocker
Congestive heart failure	Angiotensin-converting enzyme inhibitor Angiotensin receptor blocker β-Blocker Diuretic Aldosterone antagonist
Postmyocardial infarction	Angiotensin-converting enzyme inhibitor β-Blocker Aldosterone antagonist
Chronic kidney disease	Angiotensin-converting enzyme inhibitor Angiotensin receptor blocker
Prevention of recurrent cerebrovascular accident	Angiotensin-converting enzyme inhibitor Diuretic

Comprehension Questions

30.1 A 62-year-old woman presents for a routine physical examination. She is asymptomatic and is not taking any medications. Her blood pressure is found to be 135/85 mm Hg on two readings. Review of her chart reveals that her blood pressure was 133/84 mm Hg on a visit 4 months ago for a urinary tract infection. Which of the following is the most accurate statement regarding her blood pressure?

A. Her blood pressure is normal and she is at average risk for developing hypertension.
B. She has prehypertension and is at high risk for developing hypertension.
C. She has stage 1 hypertension and should be started on a thiazide diuretic.
D. She has stage 2 hypertension and should be started on multidrug therapy.

30.2 A 66-year-old woman has an average blood pressure of 150/70 mm Hg despite appropriate lifestyle modification efforts. Her only other medical problems are osteoporosis and mild depression. Her last lipid panel revealed a total cholesterol of 160 mg/dL, high-density lipoprotein (HDL) 40 mg/dL, and low-density lipoprotein (LDL) 90 mg/dL. Which of the following would be the most appropriate treatment at this time?

A. Lisinopril (Prinivil, Zestril)
B. Propranolol (Inderal)
C. Amlodipine (Norvasc)
D. Hydrochlorothiazide
E. Clonidine (Catapres)

30.3 A 48-year-old type 2 diabetic man has had persistent blood pressure readings of 150/95 mm Hg for the past 6 months. Current medications include glyburide and metformin. His last HbA1c was 6.9% and the patient has a BMI of 24. On physical examination position sense is intact but a peripheral neuropathy is detected in a stocking and glove pattern. Vibratory sensation is decreased bilaterally on both lower extremities. Eye examination shows mild papilledema but no cotton wool spots. When questioned, he says that he still occasionally sneaks a cookie after dinner and drinks alcohol nightly. Which of the following is the most appropriate treatment for him?

A. DASH diet and recheck blood pressure in 3 months
B. Thiazide diuretic alone
C. Angiotensin-converting enzyme inhibitor alone
D. Combination of angiotensin-converting enzyme inhibitor and thiazide diuretic

30.4 At a routine check-up a 6-year-old boy is found to have a blood pressure of 130/90 mm Hg. Repeated blood pressure readings are consistently elevated. The child was delivered at 36 weeks by normal spontaneous vaginal delivery with no complications. All major milestones were met on time and he currently is enrolled in first grade. The child has been healthy up until this point. Which of the following is the most appropriate diagnosis and therapeutic step?

A. The child has essential hypertension and should be started on the DASH diet.
B. The child most likely has hyperthyroidism and should be started on a β-blocker while thyroid studies are performed.
C. The child most likely has renal parenchymal disease and should have a urinalysis and renal ultrasound ordered.
D. The child most likely has "white coat" hypertension and the readings should be ignored if there is no family history of hypertension.
E. The child most likely has a pheochromocytoma and should start a 24-hour urine collection for metanephrines.

ANSWERS

30.1 **B.** This patient's blood pressure falls in the prehypertensive range. She is at increased risk for developing hypertension and may benefit from the institution of lifestyle modifications to try to reduce her risk of progression.

30.2 **D.** Randomized, placebo-controlled trials have shown that isolated systolic hypertension in the elderly responds best to diuretics, and to a lesser extent β-blockers. Diuretics are preferred, although long-acting dihydropyridine calcium channel blockers may also be used. In this case, β-blockers or clonidine may worsen the depression. Thiazide diuretics may also improve osteoporosis, and would be the most cost-effective and useful agent in this instance.

30.3 **D.** This patient's blood pressure goal is less than 130/80 mm Hg. He is greater than 20/10 mm Hg above this goal, so a combination of medications is the most appropriate initial therapy regardless of BMI or HbA1c. Refractoriness for 6 months symbolizes that he is past the point of management with diet and exercise.

30.4 **C.** Essential hypertension is rarely found in children less than 10 years of age and should be a diagnosis of exclusion. The most common cause of hypertension is renal parenchymal disease, and a urinalysis, urine culture, and renal ultrasonography should be ordered for all children presenting with hypertension.

Clinical Pearls

- Check every adult patient's blood pressure at every office visit.
- Thiazide diuretics should be the first-line drug treatment in almost all cases of hypertension. There should be a compelling reason to use another agent before a thiazide.
- All patients with hypertension are at risk for cardiovascular and cerebrovascular disease. Be sure to address their other significant risks for these diseases, including lipids, smoking, diabetes, and obesity.

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Case 31

The mother of a 12-month-old male infant calls you at midnight stating that her son has been crying incessantly for the last 6 hours. His bouts of crying last for about 20 minutes, then completely disappear for 15 minutes at a time. Since early afternoon the child has not been eating much and he has started to vomit the small amounts of juice and milk he had ingested. She decided to call you because the vomitus is now green and the bouts of crying seem to be getting worse.

In the emergency room, you recall that the patient does not have any past medical history, was born at term without complications, and is up to date on immunizations. On examination his temperature is 100°F (37.7°C), his respiration rate is 40 breaths per minute, his pulse is 155 bpm, his blood pressure is 109/60 mm Hg, and his weight is 22 lb. He cries inconsolably for 15 minutes, drawing his legs up to his chest, then becomes quiet. You notice he still produces tears, and his mucosae are moist. Heart and lung examinations are normal; abdominal examination reveals markedly decreased bowel sounds with generalized tenderness to palpation. You feel a sausagelike mass in the right side of the abdomen. His diaper holds some amount of bloody stool mixed with mucus. The rest of the examination is normal.

- What is the most likely diagnosis?
- What is the next diagnostic step?
- What are the possible complications?

ANSWERS TO CASE 31:
Abdominal Pain and Vomiting in a Child

Summary: This is a 12-month-old infant who had the sudden onset of intermittent crying with vomiting that later became bilious. As the day progressed, his bouts of pain became more severe, each lasting about 20 minutes. On examination, the infant does not yet reveal signs of hypovolemia, sepsis, or shock. On palpation of the abdomen, there is generalized tenderness and a sausagelike mass on the right side. Even though not mentioned by the parent, there is a small amount of bloody-mucous stool that is best described as "currant jelly." This patient has an intussusception that has progressed to an obstruction, and is at risk for perforation with ensuing shock and sepsis.

- **Most likely diagnosis:** Intestinal obstruction caused by intussusception.
- **Next diagnostic step:** Abdominal plain x-rays to rule out perforation.
- **Possible complications:** If perforation occurs, rapid deterioration as a consequence of shock/sepsis.

ANALYSIS

Objectives

1. Become familiar with the most likely causes of intestinal obstruction in the pediatric population.
2. Learn to differentiate between life-threatening abdominal emergencies and urgent conditions.
3. Have a diagnostic approach to the pediatric patient presenting with abdominal pain and vomiting.

Considerations

This 12-month-old infant initially presented with vomiting and intermittent abdominal pain. His vomitus was initially the gastric contents of what he had ingested, but later became bilious, which is suggestive of intestinal obstruction. The description of his abdominal pain tends to reveal the pathophysiologic nature of intussusception. The intermittency and "pain-free" intervals correlate with the gradual and slow telescoping of the intussusceptum (proximal or leading part of the intestine) into the intussuscipiens (distal or receiving end of the intestine). As the "telescoping" progresses, the portions of bowel that are trapped within the lumen of the intestine become edematous, which will ultimately lead to obstruction, ischemia, and perforation of the

bowel wall. Malrotation with volvulus will also present with a clinical picture of obstruction, and it may be difficult to differentiate among the two solely on clinical findings.

The sausage-shaped mass felt on examination will not be present in all cases. It represents the portions of bowel that are involved and have become edematous. Another common condition that may reveal a palpable mass is that of pyloric stenosis, with an olive-shaped mass sometimes palpable in the right upper quadrant of epigastrium. However, pyloric stenosis presents in younger patients and does not involve bouts of severe pain. "Currant jelly" stools are basically a mixture of blood and mucus that has sloughed from the affected bowel wall. This is not present in all cases.

Before proceeding to diagnostics, the patient should be stabilized with IV fluid hydration and surgery consultation should not be delayed. A nasogastric tube may need to be placed if obstruction is suspected. A plain film of the abdomen is done to rule out perforation. If perforation has occurred, surgical intervention is required. If no perforation is evidenced, an ultrasound of the abdomen may reveal a "coiled spring" lesion, which reflects layers of intestine within the lumen of a different portion of intestine. However, a **barium enema will be both diagnostic and therapeutic in the case of intussusception.** Although barium is widely used, a water-soluble contrast is preferred if perforation is suspected, because it will not be as irritating to the peritoneum. The therapeutic value of the enema is a result of the constant application of hydrostatic pressure on the intussusceptum, mechanically forcing it to telescope back. Air reduction may also be achieved. This method requires fluoroscopic visualization of bowel-gas patterns until reduction of the intussusceptum is seen. Barium or air reduction is effective in 75% to 90% of cases, after which a 12 to 24-hour observation period is needed until bowel function is adequate and a bowel movement has been produced. The risk of recurrence in this patient with idiopathic intussusception is approximately 10%.

APPROACH TO
Pediatric Abdominal Pain with Vomiting

DEFINITIONS

INTUSSECEPTION: A telescoping of the intestine within itself leading to abdominal pain, fever, vomiting, and ultimately bowel necrosis if not resolved.

HYPERTROPHIC PYLORIC STENOSIS: Condition of hypertrophy of the pylorus leading to gastric outlet obstruction, commonly manifesting in infants at about 1 month of age.

CLINICAL APPROACH

The most important aspect of a diagnostic approach in these cases is to be able to rapidly determine whether or not the condition is an emergency. Although the case presented is that of the most common abdominal emergency among the pediatric population, it is by no means the most common cause of intestinal obstruction. **Among the diagnoses that have to be entertained are hypertrophic pyloric stenosis, malrotation with volvulus/obstruction, foreign-body ingestion, and poisoning.**

Etiologies

As described, **intussusception will present with intermittent, severe abdominal pain, associated with vomiting that becomes bilious as obstruction sets in.** The finding of an elongated mass along the right abdomen is very suggestive of this diagnosis. The location of the mass is because most idiopathic intussusceptions occur at the ileocecal junction. They may be entirely in the jejunum, between the jejunum and ileum, or entirely colonic. Currant jelly stool is most often used to describe the finding in this condition and it correlates with the ongoing bowel ischemia as the intussusception and edema progress.

Hypertrophic pyloric stenosis is the most common cause of GI obstruction. It occurs in approximately 3 in 1000 live births, with a male-to-female ratio of 4:1. The usual presenting age is 3 to 6 weeks old, and is often described as a "hungry baby" with projectile vomiting. Vomiting is nonbilious and occurs immediately after meals. The infant will demand to be refed immediately. On examination, there may be an **olive-shaped mass felt in the right upper quadrant, and peristaltic waves may be seen across the upper abdomen moments before emesis occurs.** Ultrasonography shows the thickened pyloric muscles that are causing a gastric outlet obstruction. An upper GI contrast study usually reveals an elongated pyloric canal and a "double-track sign," which is explained by two thin tracts of barium that are created by compressed pyloric mucosa. Once the diagnosis is made, surgical referral is indicated as it is the definitive management. Because of the early age and dramatic nature of the symptoms, parents will usually seek help before the infant becomes severely ill from not eating.

Malrotation occurs in about 1 in 500 live births, but becomes symptomatic in only 1 in 6000 live births. Approximately **60% of patients will be younger than 1 month of age,** with approximately 10% presenting after 1 year of age, even into adulthood. Because it is primarily a defect that occurs during embryogenesis, the mesentery that is formed will have an abnormally narrow base, which allows the small bowel to move more freely than normal. This creates a problem when the intestinal attachment to the mesentery twists around itself, creating a volvulus. Once obstruction occurs, the **child will present with bilious vomiting and abdominal pain.** If diagnosis is delayed,

the involved segments of bowel will eventually become necrotic, leading to fluid losses and sepsis. The diagnostic approach in such cases will depend on the stability of the patient. If the patient is hypovolemic, hypotensive, has GI blood loss, or has signs of peritonitis, quick stabilization with surgical intervention is necessary. However, if the patient is hemodynamically stable, imaging can be performed to confirm a diagnosis. **If malrotation is suspected, an upper GI series is the test of choice.** In 75% of patients, the diagnosis will be clearly seen. Diagnostic findings on an upper GI are an obviously misplaced duodenum, or a duodenal obstruction with the classic "beaklike" appearance of the contrast medium caused by a volvulus. Surgery is the only treatment. Although different surgical techniques are applied to prevent a recurrence, a volvulus can repeat itself in as many as 8% of patients. Malrotation can go undiagnosed if a patient never experiences symptoms from it, and older children may present with intermittent vomiting, episodes of abdominal pain, failure to thrive, or syndromes of malabsorption.

Foreign bodies also need to be considered with abdominal pain and vomiting in a pediatric patient. **Only 10% of patients that ingest a foreign body will need an intervention** either to relieve an obstruction or to prevent GI complications. Approximately 90% of patients will pass a foreign body spontaneously, and parents need only check the stool within 24 hours to confirm passage. Sometimes, if an object can be seen on plain radiographs, a repeat x-ray within 24 hours can be done. **Among objects that require immediate intervention are flat disk, or "button," batteries in the esophagus.** These batteries will conduct electricity when both poles are in contact with the esophageal wall, which will lead to perforation. Sharp objects also need to be removed. As a general rule, any foreign body in the esophagus needs to be removed in less than 24 hours by upper endoscopy. If a sharp or elongated object (>6 cm) has already passed through the stomach and duodenum, daily x-rays should be done to follow the progress of the object. Those that do not advance within 3 days will require surgical intervention for removal.

Poisoning cannot be overlooked in the evaluation of a child with vomiting and abdominal pain. Among the multiple agents most commonly associated with hospital visits are over-the-counter (OTC) analgesic drugs, cold remedies, insecticides, pesticides, personal care products, and fumes. In a child who presents with vomiting and abdominal pain, a cholinergic syndrome is likely. It is characterized by salivation, lacrimation, diarrhea, vomiting, diaphoresis, intestinal cramps, and seizures. Insecticides and nicotine are among the agents that may induce these symptoms. Antihistamines or tricyclic antidepressants produce dry skin, dry mucosae, urinary retention, and decreased bowel sounds (anticholinergic syndrome). Some medications and substances are radiopaque, such as iron tablets, mercury, lithium, tricyclic antidepressants, Play-Doh, and enteric-coated aspirin. Finding the likely agent of poisoning will mostly depend on the history given.

Treatment

Surgical intervention will almost always be necessary if an anatomical/mechanical defect of the GI tract is present. Intestinal obstruction puts a patient at risk for perforation, which further deteriorates a patient's condition. A nasogastric tube is recommended in cases where obstruction has set in and the patient is ill. Careful monitoring of the patient's fluid status is required because of the likelihood of third spacing into ischemic bowel and decreased oral intake.

Comprehension Questions

Match the following etiologies (A—F) to the clinical vignette [31.1-31.6]:

A. Malrotation with intermittent volvulus
B. Intussusception
C. Insecticide ingestion
D. Esophageal foreign body
E. Pyloric stenosis
F. Volvulus

31.1 A 6-year-old boy left alone for 10 hours, now with hematemesis and pneumomediastinum on chest x-ray.

31.2 A 3-week-old male infant with 2 days of projectile, nonbilious vomiting and constant feeding.

31.3 A 7-year-old boy with three episodes of severe abdominal pain and vomiting in the last month, previously diagnosed with failure to thrive.

31.4 An 8-month-old girl with bilious vomiting, constant abdominal pain for 12 hours, and upper GI study showing beaklike appearance of contrast.

31.5 An 11-month-old boy with intermittent bouts of crying and nonbilious vomiting, with a history of Meckel diverticulum. A small, elongated mass is felt on right side of his abdomen.

31.6 A 4-year-old girl with profuse vomiting, sweating, lacrimation, and diarrhea, who seizes in the emergency room.

ANSWERS

31.1 **D.** The presence of blood in the vomitus and a pneumomediastinum point to an esophageal perforation, most likely from a foreign body in the esophagus.

31.2 **E.** The young age and presence of projectile, nonbilious vomiting after feeding are the keys to this diagnosis. The diagnosis of pyloric stenosis is much more common in males than females.

31.3 **A.** This is the presentation of a malrotation that did not cause enough symptoms at a younger age to lead to a diagnosis.

31.4 **F.** An infant with bilious vomiting and abdominal pain has a volvulus until proven otherwise. The upper GI study is diagnostic of this condition.

31.5 **B.** The intermittent nature of the symptoms and the palpable mass are highly suggestive of intussusception.

31.6 **C.** These symptoms are characteristic of a cholinergic syndrome, possibly caused by insecticide or nicotine poisoning.

Clinical Pearls

- Most foreign-body ingestions by children will pass spontaneously, but button batteries and sharp objects in the esophagus should be removed endoscopically.
- The risk of accidental poisoning with common household products and over-the-counter medications should be a routine part of the anticipatory guidance that occurs in a well-child visit.
- When a child appears critically ill, do not delay your resuscitative efforts or surgical consultation while you wait for laboratory tests and x-ray results.

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Case 32

An 83-year-old woman is brought to the clinic by her husband who was concerned with his wife's memory problems. He noticed some memory decline a few years ago, but the onset was subtle and did not interfere with her day-to-day activities. Mainly she has some difficulty remembering details, is repeating things, and is being forgetful. The patient's family noticed her gradually increasing memory problems, particularly over the past year. She is unable to remember her appointments and relies heavily on written notes and appointments books. Recently she got lost while driving and was found by her family 10 hours later. She was unable to use her cell phone and was unsure about her home address and phone number. She has also become more reclusive. She does not enjoy her church activities anymore and prefers to stay at home most of the time. She does not want to cook, and she is less attentive to her housework. The patient says that she has always been forgetful. Her medical history is significant for well-controlled hypertension and a history of mastectomy secondary to breast cancer diagnosed 20 years ago. She has no significant history of tobacco or alcohol use. She is independent with all activities of daily living, but needs assistance with medication administration, banking, and transportation. She is up to date with her health maintenance and immunization. Her vital signs and general physical examination are normal.

- What is the most likely diagnosis?
- What office testing can help to determine a diagnosis?
- What laboratory testing and imaging studies are indicated at this time?

ANSWERS TO CASE 32:
Dementia

Summary: An 83-year-old woman is noted by her family to have increasing memory difficulties at home. She is forgetful, repeats questions, and does not remember conversations. She had the very significant episode of getting lost in her home town. She is seemingly unaware that there is a problem that is slowly and progressively worsening.

- **Most-likely diagnosis:** Dementia of Alzheimer type.
- **Office-based testing that may be beneficial:** Folstein Mini-Mental Status Examination is the most widely used instrument. Others available include the Clock Test, the Short Portable Mental Status Questionnaire and the Mini-Cog Test. In addition, a screening test for depression should be performed.
- **Laboratory testing and imaging studies:** Screening for vitamin B_{12} and hypothyroidism. Syphilis screening if there is a risk factor or evidence of prior infection, or if patient lives in an area of high incidence. Noncontrast head computed tomography (CT) scan or magnetic resonance imaging (MRI).

ANALYSIS

Objectives

1. Develop a differential diagnosis for dementia.
2. Learn how to appropriately evaluate a complaint of memory loss.
3. Learn about treatment of Alzheimer dementia, the most common specific diagnosis of dementia.

Considerations

This 83-year-old woman is noted by her family to have progressive decrease in cognitive function. She is forgetful, gets lost easily, and this has been slowly but steadily worsening. The most likely diagnosis is dementia; however, other conditions should be considered in the differential diagnosis such as medications, stroke, thyroid disorders, chronic syphilis, or other metabolic conditions. Depression can also present as dementia at times. The workup for this patient includes a careful history and physical examination, imaging of the brain, and selective laboratory tests such as TSH, vitamin B_{12} level, CBC, and comprehensive metabolic panel. Screening for syphilis should also be considered.

APPROACH TO Dementia

DEFINITION

EXECUTIVE FUNCTIONS: High-level cognitive abilities that control other, more basic, abilities. Executive functions include the ability to start and stop behaviors, alter behaviors to fit circumstances, and adapt behaviors to new situations.

CLINICAL APPROACH

The **essential features of the diagnosis of dementia are a memory loss and impairment of executive function.** Dementia is a clinical diagnosis that can go unrecognized until it is in an advanced stage. **Patients rarely report memory loss;** the informants are usually their family members. However, relatives may fail to recognize signs and symptoms of dementia because many have a tendency to think that memory loss can be a part of normal aging. Studies of aging have showed that nonverbal creative thinking and new problem-solving strategies may decline with age, but information, skills learned with experience, and memory retention remain intact.

Clinicians should assess cognitive function whenever cognitive impairment or deterioration is suspected. These concerns may be based upon direct observation, patient report, or concerns raised by family members, friends, or caretakers. Patients with dementia may have difficulty with one or more of the following:

- Learning and retaining new information (rely on lists, calendars)
- Handling complex tasks (banking, bills, payments)
- Reasoning (adapting to unexpected situations, unfamiliar environment)
- Spatial ability and orientation (getting loss driving, walking)
- Language (word finding, repetition, confabulation)
- Behavior (agitation, confusion, paranoia)

The evaluation of a patient with suspected dementia should include a mental status examination. The **Folstein Mini-Mental Status Examination** (MMSE) is the most widely used tool in the screening for dementia. The sensitivity of the MMSE for dementia is as high as 92% and the specificity is as high as 96%. The interpretation of the score depends on the patient's education level. It is most accurate in those with at least a high school education.

Another valuable test that can be used in a busy primary care setting is the **Clock Test.** The patient is asked to draw a clock with a specific time. The patient must then accurately draw the clock face with the "big hand" and "small hand" in the correct positions. It is quick, easy to administer, and evaluates

executive function in multiple cognitive domains. Other cognitive screening tests, such as the Short Portable Mental Status Questionnaire, Modified MMSE, and Mini-Cog (three-item recall combined with clock drawing) are less popular in primary care setting.

In the evaluation of dementia, it is necessary to get information from people who know the patient well. Useful information can be obtained from informant-based functional tests, such as the Functional Activities Questionnaire (FAQ), the Instrumental Activities of Daily Living (IADL), and Caregiver Burden assessments. This information can be important for physicians and families in making plans for long-term care.

ALZHEIMER DISEASE

Alzheimer disease is the most common cause of dementia. Although a definitive diagnosis can only be made by the presence of neuritic plaques and neurofibrillary tangles detected on autopsy, clinical diagnostic criteria have been developed (Tables 32–1 and 32–2). **Common diagnostic criteria include the gradual onset and progression of cognitive dysfunction in more than one area of mental functioning that is not caused by another disorder.**

The initial evaluation includes a detailed history, from both the patient and another informant (usually a spouse, child, or other close contact) and complete physical and neurologic examinations to evaluate for any focal neurologic deficit that may be suggestive of a focal neurologic lesion. **A validated test, such as the MMSE, should be used to confirm the presence of dementia.** The results of this test can also be used to follow the clinical course, as a reduction in score over time is consistent with worsening dementia.

Table 32–1 DSM-IV CRITERIA FOR ALZHEIMER DISEASE

Development of multiple cognitive deficits manifested by both memory impairment and one of the following:
1. Aphasia: Loss of word comprehension ability.
2. Apraxia: Loss of ability to perform complex tasks involving muscle coordination.
3. Agnosia: Loss of ability to recognize and use familiar objects.
The deficits above are a decline from previous functioning and cause significant impairment in social or occupational functioning.
The course is of gradual onset and continuing decline.
The deficits are not due to other central nervous system, systemic or substance-induced conditions that cause deficits in cognition.
The disturbance is not accounted for by another psychiatric diagnosis.

Adapted from American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 4th ed. Washington, DC: American Psychiatric Association; 1994.

Table 32–2 CRITERIA FOR ALZHEIMER DISEASE

Dementia confirmed by clinical and neuropsychological examination.
Problems in at least two areas of mental functioning.
Progressive worsening of memory and mental functioning.
No disturbances of consciousness.
Symptoms beginning between ages 40 and 90 years, usually after age 65 years.
No other disorder that could cause the dementia.

Data from www.ninds.nih.gov.

A focused evaluation to rule out other causes of dementia must be performed as well. **Depression in the elderly can present with symptoms of memory disturbance.** This is known as "pseudodementia." As depression is common and treatable, a screening test for depression should be performed when dementia is evaluated. Similarly, hypothyroidism and vitamin B_{12} deficiency are common and treatable conditions that can cause cognitive problems. Thyroid-stimulating hormone (TSH) and vitamin B_{12} levels should be performed as a routine part of the workup. Neurosyphilis could present in this fashion, but is such an uncommon diagnosis that routine screening would not be recommended. Evaluation for neurosyphilis would be warranted if there were identified high-risk factors, history of the disease, or if the patient lived in an area with a high prevalence of syphilis. Neuroimaging with either a noncontrast CT scan or an MRI of the brain is recommended to rule out other confounding diagnoses. Other testing, such as positron emission tomography (PET), genetic testing, and spinal fluid analysis are not routinely recommended.

When the diagnosis of Alzheimer disease is made, a comprehensive care plan should be initiated. **The management of Alzheimer disease must be directed both at the patient and at the patient's family or caregivers**. The goals of therapy are to maximize the cognition, delay functional decline, and prevent or improve the behavioral disturbances.

Table 32–3 lists the medications that are primarily used in the treatment of Alzheimer disease. Family members should understand that the **medications may delay the progression of the disease but may not reverse any decline that has already occurred.** For that reason, the medications may be more beneficial if started earlier in the course of the disease. Antipsychotic medications have also been used to control hallucinations and agitation in patients with Alzheimer disease. However, this is an "off-label" use of medication and recent data show a higher death rate associated with the use of the newer antipsychotics. The FDA has placed a black-box warning against the use of antipsychotic medications for dementia-related psychosis due to the increased risk of deaths.

Table 32–3 MEDICATIONS USED IN THE TREATMENT OF ALZHEIMER DEMENTIA

CHOLINESTERASE INHIBITORS	INDICATIONS	SIDE EFFECTS/COMMENTS
Donepezil (Aricept)	Mild-moderate Alzheimer dementia	Common: nausea, vomiting, diarrhea, dizziness, headaches
Galantamine (Razadyne)	Mild-moderate Alzheimer dementia	Severe: arrhythmias, dementia bradycardia, urinary obstruction
Rivastigmine (Exelon)	Alzheimer dementia	
Tacrine (Cognex)	Alzheimer dementia	All of above side effects; risk of hepatotoxicity—must frequently monitor liver enzymes
N-methyl-D-aspartate (NMDA) antagonist Memantine (Namenda)	Moderate-severe Alzheimer dementia	Side-effect profile comparable to placebo; can be used in combination with cholinesterase inhibitors

Behavioral interventions also may be beneficial. These can include scheduled toileting in an effort to reduce episodes of incontinence, writing reminder notes, keeping familiar objects around, providing adequate lighting, and making duplicates of important objects (eg, keys) in case they get lost. Caregivers also need support and may benefit from appropriate training, support groups, and periodic respite care.

Unfortunately, even with the best of care, Alzheimer disease is relentless and progressive. Families may have significant difficulties and conflicts regarding issues surrounding end-of-life care and placement in assisted living or nursing homes. Resources such as local chapters of the Alzheimer Association (www.alz.org) may provide valuable services, information, and support.

VASCULAR DEMENTIA

Vascular dementia, or multi-infarct dementia, is the second most common cause of dementia. In vascular dementia, there is neuronal loss as a consequence of one or more strokes. The **symptoms are related to the amount and location of the neuronal loss**. Vascular dementia can exist along with Alzheimer disease or other causes of dementia, resulting in a mixed-dementia syndrome. Unlike Alzheimer disease, which is a gradually progressive process, **vascular dementia often has a sudden onset and progresses in a stepwise**

fashion. Patients tend to function at a certain level and then show an acute deterioration when the initial, or subsequent, infarcts occur. The risk factors include those for cerebrovascular disease (hypertension, tobacco use, diabetes, etc). There are no controlled trials showing medication effectiveness in vascular dementia, so the treatment is aimed at reducing the risk of further neurologic damage.

OTHER ILLNESSES ASSOCIATED WITH DEMENTIA

Numerous other conditions may present with dementia or have dementia as a prominent symptom. **Parkinson disease** commonly has an associated dementia, especially as the overall disease advances. **Normal pressure hydrocephalus** causes the triad of dementia, gait disturbance, and urinary incontinence. **Lewy body** dementia has symptoms similar to Alzheimer disease, but the dementia has a fluctuating course and is often accompanied by hallucinations early in the course of the disease. Dementia can be a complication of **chronic alcohol abuse,** reinforcing the need for a complete history of substance use. Many **prescription and over-the-counter medications** can cause memory disturbances. Chief among these are anticholinergic medications, sedatives (benzodiazepines), sleeping pills, and narcotic pain medications. As noted previously, hypothyroidism, vitamin B_{12} deficiency, and neurosyphilis may present as dementing illnesses. **Metabolic abnormalities,** such as hyponatremia or abnormal calcium levels, and other infections, such as **AIDS,** can also cause dementia.

DELIRIUM

Delirium is an **acute change in mental status that is characterized by fluctuations in levels of consciousness.** It is usually caused by an acute medical illness, the use of a medication, or the withdrawal from a drug or alcohol. Delirium affects 10% to 30% of hospitalized patients, with a higher incidence in the elderly, in those with an underlying dementia, and in those with multiple underlying medical conditions. **The treatment of delirium is treatment of the condition that precipitated it.** Delirium is often reversible if the underlying cause can be found and aggressively managed. Patients with delirium have significantly longer hospital stays and increased mortality rates.

Comprehension Questions

32.1 A 63-year-old man is brought in by his family because of memory loss. They have noted a worsening of his symptoms over several months. They also report that he has had multiple falls, hitting his head on one occasion, and has had frequent urinary incontinence. On examination a gait apraxia is noted. Which of the following is the most likely diagnosis?

A. Alzheimer disease
B. Normal pressure hydrocephalus
C. Dementia with Lewy bodies
D. Delirium

32.2 An 82-year-old woman is admitted to the hospital for a urinary tract infection (UTI). On the second hospital day, her family says that she has been confused and falling asleep frequently while in the hospital. She has been hallucinating—talking to people who are not in the room. They report that prior to this illness, she was independent and "sharp as a tack." Which of the following is the most appropriate treatment?

A. Start rivastigmine (Exelon) for worsening of Alzheimer dementia.
B. Change her antibiotic, as she is likely having an allergic reaction.
C. Optimize your medical treatment of her infection and any other medical conditions.
D. Give her a dose of ziprasidone (Geodon) for her hallucinations.

32.3 A 77-year-old man is brought to your office by his wife, who states that he has been having mental difficulties in recent months, such as not being able to balance their checkbook or plan for his annual visit with the accountant. She also tells you that he has reported seeing animals in the room with him that he can describe vividly. He takes frequent naps and stares blankly for long periods of time. He seems almost normal at times, but randomly appears very confused at other times. He has also been dreaming a lot and has fallen down more than once recently. He currently takes aspirin, 81 mg/d. On examination, the patient walks slowly with a stooped posture and almost falls when turning around. He has only minimal facial expressiveness. No tremor is noted and the remainder of the examination is normal. He is able to recall three words out of three, but clock drawing is abnormal. Laboratory studies are normal and a CT of the brain shows changes of aging. What type of dementia does this patient most likely have?

A. Dementia with Lewy bodies
B. Alzheimer disease
C. Frontotemporal dementia
D. Vascular dementia
E. Dementia of Parkinson disease

32.4 A 66-year-old woman is brought in by her family because of difficulty with memory and disorientation that has worsened over the past 6 months. A careful history and physical examination is performed. Which of the following tests is most appropriate in this patient?

A. Head CT or MRI
B. Lumbar puncture
C. Rapid plasma reagin (RPR)
D. Electroencephalogram (EEG)

ANSWERS

32.1 **B.** Normal pressure hydrocephalus classically causes dementia, incontinence, and gait disturbance. All of the other listed conditions may cause memory disturbance, but the constellation of these three symptoms is most consistent with normal-pressure hydrocephalus.

32.2 **C.** This scenario is one that is commonly seen in hospitals and is consistent with delirium. The patient is elderly and has an infection, causing both an acute change in her mental status and a fluctuating level of consciousness. The treatment is to treat the underlying infection and any associated medical conditions.

32.3 **A.** This patient has dementia with Lewy bodies, which is the second most common histopathologic type after Alzheimer disease. He demonstrates typical signs and symptoms, including well-formed hallucinations, vivid dreams, fluctuating cognition, sleep disorder with periods of daytime sleeping, frequent falls, deficits in visuospatial ability (abnormal clock drawing), and REM sleep disorder (vivid dreams). In Alzheimer disease, the predominant early symptom is memory impairment without the other symptoms found in this patient. In dementia of Parkinson disease, extrapyramidal symptoms such as tremor, bradykinesia, and rigidity precede the onset of memory impairment by more than 1 year. Frontotemporal dementia presents with behavioral changes, including disinhibition, or language problems such as aphasia.

32.4 **A.** A noncontrast head CT or MRI is recommended by the American Academy of Neurology for the routine evaluation of dementia. All of the other tests may be appropriate if there is a finding on the history or examination that calls for further testing (an exposure to syphilis, episodes suggestive of seizures, or symptoms of normal pressure hydrocephalus for which a spinal tap may be performed).

Clinical Pearls

- The presentation of acutely altered mental status (delirium) should prompt an aggressive workup for an underlying cause, as treatment may result in correction of the mental status.
- Alzheimer disease is a disease of the family, not just the individual. It is critical to treat the patient while giving support to the caregivers.

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Case 33

A 20-year-old woman comes to clinic for an annual physical examination. She has no complaints. She has no significant medical or surgical history. She is currently taking oral contraceptive pills because of her irregular menstrual cycles. She attained menarche at age 13 years and has had irregular cycles since. She has never been sexually active. Her family history is positive for hypertension and obesity in both her parents. On examination, her blood pressure is 120/85 mm Hg, her pulse is 78 bpm, and her respiratory rate is 14 breaths per minute. Her weight is 188 lb and she is 63 in tall. Her physical examination is unremarkable except for a brownish/black, velvety thickening of the skin on the back of her neck, hirsutism, and abdominal obesity.

- What are the clinical issues that need to be addressed during this preventive visit?
- What is your next step in the evaluation of this patient?
- What are the therapeutic options available for this patient?

ANSWERS TO CASE 33:
Obesity

Summary: A 20-year-old obese woman presents for a routine examination. Along with her abdominal obesity, she has irregular menstrual cycles, acanthosis nigricans, and hirsutism.

- **Clinical issues to address:** Obesity and possible polycystic ovarian disease.
- **Next steps in evaluation:** Calculate a body mass index (BMI), measure waist circumference, repeat blood pressure. Order laboratory tests to measure fasting glucose, lipids, thyroid-stimulating hormone (TSH), and liver enzymes.
- **Therapeutic options:** Assess her interest in losing weight. If she is interested, devise weight-loss goals and advise on diet and physical activity to achieve these goals. If she is not interested, advise on the health benefits of weight loss and address other risk factors. In either case, arrange follow-up. At subsequent visits, can consider adding pharmacotherapy as an adjunct to diet and exercise.

ANALYSIS

Objectives

1. Understand the etiology and pathogenesis of obesity.
2. Know other comorbid conditions associated with obesity.
3. Learn the diagnostic criteria for obesity and the metabolic syndrome.
4. Understand the therapeutic options available for the management of obesity.

Considerations

Obesity is a chronic and stigmatizing disease that begins early in life. Routine physical examination visits serve as a good platform to address issues related to obesity and its associated comorbid conditions. In this case, this visit should be taken as an opportunity to address obesity and its management.

Increased body weight is a major risk factor for the development of disease and for premature death. In National Health and Nutritional Examination Surveys (NHANES) III, the metabolic syndrome was present in 5% of those at normal weight, 22% of those who were overweight, and 60% of those who were obese. The metabolic syndrome is an important risk factor for subsequent development of type 2 diabetes and cardiovascular disease.

In this case, this patient's BMI is 33.5. Further measurements included a waist circumference of 36 in and a repeat blood pressure of 125/85 mm Hg.

Her laboratory test results included total cholesterol of 202 mg/dL, high-density lipoprotein (HDL) cholesterol of 35 mg/dL, low-density lipoprotein (LDL) cholesterol of 120 mg/dL, and triglycerides of 172 mg/dL. Her fasting glucose was 104 mg/dL, and she had normal renal and liver function tests. She has metabolic syndrome based on her abdominal circumference, increased triglycerides, low HDL, and mildly elevated LDL cholesterol levels. She may also need further investigation for the presence of polycystic ovarian syndrome (PCOS) because of her obesity and history of irregular cycles.

Both the metabolic syndrome and PCOS are very closely associated with obesity and insulin resistance. In this situation, the key clinical implication of these diagnoses is identification of a patient needing aggressive lifestyle modification focused on weight reduction and increased physical activity.

APPROACH TO Obesity

DEFINITIONS

BODY MASS INDEX (BMI): A measurement of the relative composition of lean body mass and body fat; calculated as weight in kilograms/(height in meters)^2.

METABOLIC SYNDROME: A state of insulin resistance characterized by abdominal obesity, dyslipidemia, elevated blood pressure, and impaired fasting glucose.

OBESITY: An excessive amount of body fat, which increases the risk of medical illness and premature death.

SATIATION: Level of fullness during a meal.

SATIETY: Level of hunger after a meal.

CLINICAL APPROACH

Obesity is a chronic and easily diagnosed disease that is associated with life-threatening morbidity and mortality. Overall, **recent data show that 33.3% of adult men, 35.3% of adult women, and 16% of 2- to 19-year-olds were obese.** Approximately 300,000 deaths are attributed to obesity each year with the direct and indirect costs exceeding $100 billion per year.

Diagnostic Tools

BMI is used as a quick and easy measure of overweight and obesity. However, **BMI is not an accurate measure of overweight/obesity in patients with heart failure, pregnant women, body builders, and certain ethnic groups.** Therefore, in addition to BMI, additional measurements, like waist circumference, hip

Table 33–1 DEFINITION OF OBESITY BASED ON BMI

	BMI (KG/M^2)	OBESITY CLASS
Underweight	<18.5	
Normal	18.5-24.9	
Overweight	25.0-29.9	
Obesity	30.0-34.9	I
	35.0-39.9	II
Extreme obesity	>40	III

circumference, and waist-to-hip ratio, need to be used to accurately identify the population at risk. Direct measurement of percentage of body fat may also provide additional information. Table 33–1 lists the classification of overweight/obesity based on BMI.

Along with the measurements mentioned above, a physical examination and **focused laboratory workup** should be performed to look for complications and comorbid conditions. A **fasting glucose** level should be measured to evaluate for diabetes mellitus and impaired glucose tolerance. The presence of acanthosis nigricans—a velvety, hyperpigmented thickening of the skin commonly found on the neck and axillary regions—may also be a sign of insulin resistance. **Fasting lipids** should also be measured, both to evaluate for the presence of metabolic syndrome and for the assessment of the patient's risk for cardiovascular disease. **TSH** should be measured to screen for hypothyroidism. **Liver enzymes** should be requested, as abnormal results may indicate the development of a fatty liver.

Pathogenesis

Energy balance is the relationship of energy intake to energy expenditure. When more energy is expended than taken in, weight loss ensues. When the intake of energy exceeds the amount expended, weight gain occurs. In all persons, **obesity is caused by ingesting more energy than is expended over a period of time.** Energy balance is affected by both genetic and environmental factors.

It has been **estimated that genetic background can explain 40% or more of the variance in body mass in humans.** The genetic component is complex and involves the interaction of multiple genes. However, the marked increase in obesity cannot be completely attributed to genetics. An **increase in energy consumption with a decrease in physical activity is thought to be the main contributor to the current obesity epidemic.** Among numerous issues, the availability of convenience foods and the increase in palatability and serving size, compounded with industrialization leading to decreased physical activity, has led to an altered energy balance.

Health Hazards Associated with Obesity

Obesity is a risk factor for the development of numerous medical conditions (Table 33–2). The more complications that develop, the greater the mortality risk for the individual. Also, the more complications that develop, the more difficult it becomes to manage the underlying obesity. For example, a person with degenerative arthritis and heart disease may have significant symptoms during exercise, impairing his or her ability to expend more energy in an effort to lose weight.

Treatment

Treatment of obesity should begin in patients with a BMI greater than 25 or who have visceral obesity, documented by increased waist circumference or a waist-to-hip ratio greater than 0.9 in men and greater than 0.85 in women. Weight loss of as little as 5 lb reduces the risk of developing comorbid conditions. Developing a **treatment plan** for obesity is complex and should use a **combination of dietary restrictions, increased physical activity, and behavior therapy** as a gold standard.

Dietary intervention is the cornerstone of weight-loss therapy. Most diets work in two principal dimensions: energy content and nutrient composition. **A calorie deficit of 500 to 1000 cal/d produces a weight loss of 1 to 2 lb/wk.** There are different kinds of specific dietary modifications recommended, but they all work based on calorie restriction. Calorie restriction should not compromise the nutrient content of the diet; patients should still aim for a balanced meal.

Table 33–2 COMMON MEDICAL COMPLICATIONS OF OBESITY

Cardiovascular disease
Cerebrovascular disease
Cholelithiasis
Degenerative joint disease
Eating disorders
Hyperlipidemia
Hypertension
Infertility/reduced fertility
Malignancies
Menstrual cycle irregularities
Mood disorders
Polycystic ovary syndrome
Sleep apnea
Type 2 diabetes mellitus

The addition of exercise training to a diet program can add to the weight loss. However, **physical activity alone is not an effective method for achieving weight loss.** Although increasing physical activity is not effective for initial weight loss, physical activity is very important for long-term weight management. Patients should engage in moderate to vigorous physical activity for at least 30 min/d, 5 d/wk, both to maintain weight loss and for the independent health benefits of exercising.

The **purpose of behavior modification therapy is to help patients identify and modify eating and physical activity habits that contribute to obesity.** The targets of behavior modification are avoiding triggers, maintaining dietary diaries, avoidance of high-risk situations, and breaking repetitive behaviors, such as watching TV while eating.

Pharmacotherapy

Table 33–3 lists the medications commonly used in the treatment of obesity. Only sibutramine and orlistat are approved for long-term use. With the exception of orlistat, which inhibits the absorption of dietary fat, all medications approved for obesity act as anorexiants. Anorexiant medications increase satiation, satiety, or both, by affecting the monoamine system in the hypothalamus. Increasing satiation results in a reduction in the amount of food eaten, whereas increasing satiety reduces the frequency of eating.

Bariatric Surgery

Patients with a **BMI greater than 40, or greater than 35 with comorbid conditions, are potential candidates for surgical treatment of obesity.** The two most common surgeries done are Roux-en-Y gastric bypass and "lap banding." The Roux-en-Y gastric bypass involves the construction of a small (10-30 mL) gastric pouch that empties into a segment of jejunum. This is mostly a restrictive procedure, but there is some degree of associated malabsorption. In lap banding, an adjustable silicone gastric band is laparoscopically placed around the upper stomach just distal to the gastroesophageal junction. The band has a balloon connected to a subcutaneously implanted port, which can be inflated or deflated to reduce the circumference of the band. Complications of the banding procedure are less common and less severe than in gastric bypass, but the weight loss may also be less.

Metabolic Syndrome

Guidelines from the 2001 National Cholesterol Education Program (Adult Treatment Panel [ATP] III) suggest that the clinical identification of the metabolic syndrome should be based upon the presence of any three of the following traits:

Table 33–3 MEDICATIONS USED IN THE TREATMENT OF OBESITY

DRUG NAME (TRADE NAME)	MECHANISM OF ACTION	NOTES
Dextroamphetamine (Dexedrine)	Sympathomimetic (increased norepinephrine release)	All: Numerous drug interactions; stimulant side effects include insomnia, agitation, tachycardia; additive effects with other stimulants (caffeine, cold medications, etc); can be addicting; avoid with monoamine oxidase-inhibitors; all indicated for short-term use only
Phendimetrazine (Bontril)	Sympathomimetic (increased norepinephrine release)	
Diethylpropion (Tenuate)	Sympathomimetic (increased norepinephrine release)	
Phentermine (Fastin, Ionamin, Adipex-P)	Norepinephrine reuptake inhibitors	
Sibutramine (Meridia)	Serotonin-norepinephrine reuptake inhibitor	Can result in severe blood pressure elevation; should not be used in combination with selective serotonin reuptake inhibitors or triptans (increased risk of serotonin syndrome); indicated for short- or long-term use
Orlistat (Xenical, Alli)	Selective inhibitor of pancreatic lipase, results in reduced intestinal digestion of fat	GI side effects common: diarrhea, bloating, gas, oily stools; must follow low-fat diet to reduce side effects; indicated for short- or long-term use

- Abdominal obesity, defined as a waist circumference in men greater than 102 cm (40 in) and in women greater than 88 cm (35 in). ATP III recognized that some men develop multiple metabolic risk factors when waist circumference is only marginally increased (94-102 cm [37-39 in]); such patients may have a genetic predisposition to insulin resistance.
- Serum triglycerides greater than or equal to 150 mg/dL (1.7 mmol/L).
- Serum high-density lipoprotein (HDL) cholesterol less than 40 mg/dL (1 mmol/L) in men and less than 50 mg/dL (1.3 mmol/L) in women.

- Blood pressure greater than or equal to 130/85 mm Hg.
- Fasting plasma glucose greater than or equal to 110 mg/dL (6.1 mmol/L).

Current minimum estimates are that the prevalence of metabolic syndrome in the United States is at least 22%. The metabolic syndrome is an important risk factor for subsequent development of type 2 diabetes and cardiovascular disease. Thus, the key clinical implication of a diagnosis of metabolic syndrome is identification of a patient needing aggressive lifestyle modification focused on weight reduction and increased physical activity.

Comprehension Questions

33.1 A 15-year-old adolescent male is brought in to the clinic by his mother. He has been experiencing chest pain, shortness of breath, and is having increases episodes of asthma exacerbation. He is 5ft 10 in and weighs 399 lb. An ECG in the office shows a normal sinus rhythm. He is unable to participate in school athletics due to his weight and has little physical activity after school. He has friends, but has some esteem issues because of being so large. He often finds it hard to find current trendy clothes in his size, but says its ok because he is not the largest person at his school. His mother, who is also morbidly obese, is worried that he will have a heart attack and wants him to lose weight. Which of the following patients would be a candidate for bariatric surgery as initial treatment for obesity?

A. A man with a BMI of 32 and arthritis of the knees.
B. A woman with a BMI of 30 and type 2 diabetes.
C. A woman with a BMI of 42 but no identifiable complications.
D. Any obese patient who desires bariatric surgery should have it offered.

33.2 A patient you have been seeing for 10 years recently lost his health insurance because his BMI is too high. He was born with achondroplasia and is 4 ft 8 in and 192 lb. He has been in good health and takes no medications. On examination his BP is 122/ 76 mm Hg, pulse 56 bpm, and respiratory rate 16 breaths per minute. For which of the following patients is a BMI measurement most likely to be an accurate assessment of obesity?

A. A bodybuilder with a BMI of 38
B. A pregnant woman with a BMI of 31 in her 37th week of gestation
C. A man with congestive heart failure, pitting edema, and a BMI of 30
D. A hypertensive woman with a BMI of 32

33.3 A 34-year-old Hispanic woman comes to clinic to discuss weight management. She is currently 5 ft 2 in and 265 lb. She says she always had a hard time managing her weight as a child but let things get out of control when she was living on her own in college. She has had two children in the past 5 years. She gained 50 lb with the first child and lost 30 lb. With the second child she gained 35 lb and lost 10 lb. She has tried many fad diets where she initially loses weight but eventually gains it back. She exercises some but is limited by osteoarthritis of the knees. She has thought about gastric bypass but is fearful of undergoing a surgical procedure. Which of the following medications may be used for the long-term management of obesity?

A. Orlistat
B. Phendimetrazine
C. Dextroamphetamine
D. Phentermine

ANSWERS

33.1 **C.** Bariatric surgery can be effective but carries significant risks. It is indicated for people with a BMI of 40 or greater or with a BMI of 35 or greater and obesity-related complications.

33.2 **D.** A BMI reading will not accurately assess the ratio of lean body mass to body fat in highly muscled persons (weightlifters, athletes), in pregnant women, and in symptomatic congestive heart failure.

33.3 **A.** Only orlistat and sibutramine are indicated for the long-term treatment of obesity. All of the other medications should be for short-term use only.

Clinical Pearls

- Obesity is a chronic disease that is reaching epidemic status in the United States and worldwide.
- BMI is a common tool used to grade obesity but in certain cases, it may be inadequate.
- Obesity treatment should include dietary restriction, increased activity, and behavioral modifications.

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Case 34

A 33-year-old woman presents with a complaint of headaches. She has had headaches since she was a teenager but they have become more debilitating recently. The episodes occur once or twice each month and last for up to 2 days. The pain begins in the right temple or at the back of the right eye and spreads to the entire scalp over a few hours. She describes the pain as a sharp, throbbing sensation that gradually worsens and is associated with severe nausea. Several factors aggravate the pain, including loud noises and movement. She has taken several over-the-counter medications for the pain, but the only thing that works is going to sleep in a quiet, darkened room. A thorough history reveals that her mother suffers from migraine headaches. Her vital signs, general physical examination, and a thorough neurologic examination are all within normal limits.

- What is the most likely diagnosis?
- What imaging study is most appropriate at this time?
- What are the most appropriate therapeutic options?

ANSWERS TO CASE 34:
Migraine Headache

Summary: A 33-year-old woman presents with headaches that are throbbing and over her right eye. Her headaches have occurred since she was a teenager and have progressively worsened. She has not found relief from over-the-counter preparations.

- **Most likely diagnosis:** Migraine without aura.
- **Most appropriate imaging study:** No imaging is indicated at this time as there are no "red flag" symptoms or signs.
- **Most appropriate therapy:** A "triptan" medication given in a means that does not have to be swallowed (eg, subcutaneous, intranasal, or orally dissolving tablet).

ANALYSIS

Objectives

1. Know the differential diagnosis of chronic headache.
2. Learn the "red flag" symptoms and signs that should prompt rapid, specific diagnostic and treatment interventions.
3. Know how to manage common headache syndromes.

Considerations

The patient described in the case has symptoms that are very characteristic of classic migraines without aura. Her headaches are unilateral, throbbing in nature, and have been progressively worse. Migraine headaches are the most common headaches of vascular origin. They **typically cause recurrent episodes of headache, nausea, and vomiting.** They can also be associated with other neurologic symptoms such as photophobia, light-headedness, paresthesia, vertigo, and visual disturbances. In the patient described in this case, the history and lack of physical findings can reasonably lead to the diagnosis of migraine headaches without aura ("common migraine"), the most frequently occurring form. Other classifications of migraines include migraine with aura ("classic migraine"), ophthalmoplegic migraine, retinal migraine, and childhood periodic syndromes that may be precursors to or associated with migraines. During the evaluation of this patient, the focus should be on determining the etiology of the headache, assessing for any red flags (see Table 34–1) that may indicate a worse pathological causes, identifying triggers, and therapy for the condition.

Table 34–1 "RED FLAG" SYMPTOMS AND SIGNS IN THE EVALUATION OF HEADACHES

RED FLAG	DIFFERENTIAL DIAGNOSIS	WORKUP STUDIES
Sudden-onset headache	Subarachnoid hemorrhage, pituitary apoplexy, hemorrhage into a mass lesion or vascular malformation, mass lesion	Neuroimaging first; lumbar puncture if neuroimaging negative
Headaches increasing in severity and frequency	Mass lesion, subdural hematoma, medication overuse	Neuroimaging, drug screen
Headache beginning after age 50 years	Temporal arteritis, mass lesion	Neuroimaging, erythrocyte sedimentation rate level
New-onset headache in patient with risk factors for HIV infection or cancer	Meningitis, brain abscess (including toxoplasmosis), metastasis	Neuroimaging first; lumbar puncture if neuroimaging negative
Headache with signs of systemic illness (fever, stiff neck, rash)	Meningitis, encephalitis, Lyme disease, systemic infection, collagen vascular disease	Neuroimaging, lumbar puncture, serology
Focal neurologic signs or symptoms of disease (other than typical aura)	Mass lesion, vascular malformation, stroke, collagen vascular disease	Neuroimaging, collagen vascular evaluation (including antiphospholipid antibodies)
Papilledema	Mass lesion, pseudotumor cerebri, meningitis	Neuroimaging, lumbar puncture
Headache subsequent to head trauma	Intracranial hemorrhage, subdural hematoma, epidural hematoma, posttraumatic headache	Neuroimaging of brain, skull, and cervical spine

Data from South-Paul JE, Matheny SC, Lewis EL, et al. *Current Diagnosis and Treatment in Family Medicine*. New York, NY: McGraw-Hill; 2004:330.

According to the International Headache Society, symptoms diagnostic of migraine headache include **moderate to severe headache with a pulsating quality; unilateral location; nausea and/or vomiting; photophobia; phonophobia; worsening with activity; multiple attacks lasting for 4 hours to 3 days; and absence of history or physical examination findings that would make it likely that the headache is the result of another cause.** Common triggers of migraine headaches include menses, fatigue, hunger, and stress.

APPROACH TO
Migraine Headaches

DEFINITIONS

MIGRAINE HEADACHES: Vascular headaches typically throbbing unilateral in character, and may be present with or without an aura. There is a high female predominance.

TENSION HEADACHE: Typically presenting with pericranial muscle tenderness and a description of a bilateral bandlike distribution of the pain.

CLUSTER HEADACHE: Unilateral headaches that may have a high male predominance, can be located in the orbital, supraorbital, or temporal region. It is generally described as a deep, excruciating pain lasting from 15 minutes to 3 hours. These headaches are usually episodic; however a small subset may have chronic headaches.

CLINICAL APPROACH

Headaches are an extremely common complaint in primary care, urgent care, and emergency settings. The vast majority of adults have at least one headache each year, although most do not present for medical care. **The role of the practitioner is to attempt to accurately diagnose the cause of the headache, rule out secondary causes of headaches ("red flags") that may signify a serious underlying pathology, provide appropriate acute management, and assist with headache prevention when needed.**

The medical history in a patient with headaches should focus on several important areas. The quality and characteristics of the headache and its specific location and radiation should be identified. The presence of associated symptoms, especially neurologic symptoms that may suggest the presence of a focal neurologic lesion or increased intracranial pressure, must be documented. The age at which the patient first developed the headaches, the frequency and duration of the headaches, and the amount of disability and distress that is caused to the patient should be explored. It is also important to note what the patient has done to try to treat the headaches in the past, including as much detail as possible regarding medication usage (both prescription and over-the-counter [OTC]).

The examination should include both a general examination and a detailed neurologic examination. A funduscopic examination revealing papilledema may be supportive of the presence of increased intracranial pressure. **Identifying a focal neurologic deficit increases the likelihood of finding a significant CNS pathology as the cause of the headache.**

A patient with symptoms and signs consistent with migraine and who does not have any "red flag" findings (Table 34–1) does not require any further testing

prior to instituting treatment. Neuroimaging should be performed if there is an unexplained neurologic abnormality on examination or if the headache syndrome is not typical of either migraines or some other primary headache disorder. The **presence of rapidly increasing headache frequency or a history of either lack of coordination, focal neurologic symptom, or headache awakening the patient from sleep, raises the likelihood of finding an abnormality on an imaging test.** Magnetic resonance imaging (MRI) may be more sensitive than computed tomography (CT) scanning for the identification of abnormalities, but it may not be more sensitive at identifying *significant* abnormalities. Other testing (eg, blood tests, electroencephalogram [EEG]) should only be performed for diagnostic purposes if there is a suspicion based on the history or physical examination.

The treatment of headache is best individualized based on a thorough history, physical examination, and the interpretation of any additional study results. Nonpharmacologic measures and cognitive-behavioral therapy are worth considering in most patients with primary headache disorders. The US Headache Consortium lists the following general management guidelines for the treatment of migraine headaches:

- Educate migraine patients about their condition and its treatment, and educate them to participate in their own management.
- Use migraine-specific agents (eg, triptans, dihydroergotamine, ergotamine) in patients with more severe migraines, and in those whose headaches respond poorly to treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) or combination analgesics, such as aspirin plus acetaminophen plus caffeine.
- Select a nonoral route of administration for patients whose migraines present early with nausea or vomiting as a significant component of the symptom complex.
- Consider using a self-administered rescue medication for patients with severe migraine who do not respond well to other treatments.
- Guard against medication-overuse or rebound headaches. Patients who require acute treatment on two or more occasions per week should probably be on prophylactic treatment.

The goal of therapy in migraine prophylaxis is a reduction in the severity and frequency of headache by 50% or more. The strongest evidence supports the use of amitriptyline, propranolol, timolol, and divalproex sodium for migraine headache prevention.

OTHER HEADACHE SYNDROMES

Tension-Type Headache

Tension headache is the most prevalent form of primary headache disorder, typically presenting with pericranial muscle tenderness and a description of a bilateral bandlike distribution of the pain. Headaches can last from 30 minutes

to 7 days and there is no aggravation by walking stairs or similar routine physical activity. There is no associated nausea or vomiting. Photophobia and phonophobia are both absent, or one, but not the other, is present. They can be either episodic (<180 d/yr) or chronic (>180 d/yr).

Initial medical therapy of episodic tension-type headache includes aspirin, acetaminophen, and NSAIDs. Because of the significant risk of developing drug dependency or medication-overuse headache, avoiding caffeine-containing over-the-counter or prescription drugs and codeine- or ergotamine-containing preparations (including combination products) is recommended. The general management principles for the treatment of migraine headaches can also be applied to the treatment of chronic tension-type headaches. In frequent headache sufferers, the combination of antidepressant medications and stress management therapy reduces headache activity significantly. Other prophylactic treatments of chronic tension-type headaches include calcium channel blockers and β-blockers.

Cluster Headache

Cluster headache is strictly unilateral in location and can be located in the orbital, supraorbital, or temporal region. It is generally described as a deep, excruciating pain lasting from 15 minutes to 3 hours. The frequency can vary from one every other day to eight attacks per day. Cluster headaches are associated with ipsilateral autonomic signs and symptoms, and have a much greater prevalence in men. Compared to migraine sufferers who often desire sleep and a quiet, dark environment during their headache, individuals with cluster headache pace around, unable to find a comfortable position. The acute treatment of cluster headache involves 100% oxygen at 6 L/min, dihydroergotamine, and the triptans. Verapamil, lithium, divalproex sodium, methysergide, and prednisone may be used for prophylactic treatment. Because of side effects related to chronic use, methysergide and prednisone need to be used with caution.

Chronic Medical Conditions

Patients with certain underlying medical conditions have a greater incidence of having an organic cause of their headache. Patients with cancer may develop headaches as a consequence of metastases. Someone with uncontrolled hypertension (with diastolic pressures >110 mm Hg) may present with the chief complaint of headache. Patients with HIV infection or AIDS may present with central nervous system metastases, lymphoma, toxoplasmosis, or meningitis as the cause of their headache.

Medication-Related Headache

Numerous medications have headache as a reported adverse effect. Medication-overuse headache (formerly drug-induced or "rebound" headache) may occur following frequent use of any analgesic or headache medication. This includes

both nonprescription (eg, acetaminophen, NSAIDs) and prescription medications. Caffeine use, whether as a component of an analgesic or a beverage, is another culprit in this category. The duration and severity of the withdrawal headache following discontinuation of the medication vary depending on the medication(s) involved.

Comprehension Questions

34.1 A 28-year-old man presents for evaluation of headaches. He has had several episodes of unilateral throbbing headaches that last 8 to 12 hours. When they occur, he gets nauseated and just wants to go to bed. Usually they are relieved after he lies down in a dark, quiet room for the remainder of the day. He is missing significant work time due to the headaches. He has a normal examination today. Which of the following statements is accurate regarding this situation?

A. He needs a CT scan of his head to evaluate for the cause of his headache.
B. When he gets his next headache, he should breathe in 100% oxygen and use a triptan medication.
C. If he has not already done so, he should use aspirin 650 mg orally every 4 hours as needed and take a stress-management class.
D. An injectable or nasal spray triptan is most appropriate.

34.2 A 52-year-old woman presents to the office for an acute visit complaining of 2 hours of headache. She says that it came on suddenly with no account of trauma and is the worst headache she has ever had. She has had migraines since she was an early adult. The pain is described as "stabbing" and is more severe on the left side. She takes no medications and recently stopped taking oral contraceptive pills after going through menopause. Her blood pressure is elevated at 145/95 mm Hg, but otherwise she has no focal neurologic abnormalities on examination. She is alert and oriented to person, place, time, and situation. Which of the following is the most appropriate management at this time?

A. Prescribe a triptan medication.
B. Schedule a noncontrast head CT scan for tomorrow morning.
C. Call 911 and transfer the patient to the nearest emergency room.
D. Prescribe an antihypertensive medication and follow-up in 2 weeks.

34.3 A 43-year-old man presents with headaches that he has had daily for several months. Every morning at work, usually between 9 and 10 AM, he has to take 650 mg of acetaminophen to relieve the headache. This has been going on for the past 3 months and he is at the point of looking for a new job, as he thinks that job stress is the cause of his symptoms. His examination is normal. Which of the following is the most appropriate advice for him?

A. Continue with the as-needed acetaminophen and find a less stressful career.
B. He should start an antidepressant for headache prophylaxis.
C. His headaches are most likely to improve if he stops taking the acetaminophen.
D. A triptan is a more appropriate treatment for him.

ANSWERS

34.1 **D.** This patient gives a history very consistent with common migraine headaches. There are no red flags found on history or examination, so no further testing is necessary at this point. As he has significant nausea, he may benefit from nonoral medication. A triptan delivered by injection or nasal spray is a reasonable starting point for him.

34.2 **C.** The acute onset of the most severe headache in a patient's life is concerning for the presence of a subarachnoid hemorrhage. This is a medical emergency. This patient should be transported by emergency medical services to the nearest emergency facility for stabilization and management.

34.3 **C.** This situation is typical of a medication-related headache. While finding a new, less-stressful job may be beneficial, the problem will not resolve until he discontinues the daily use of his over-the-counter analgesic.

Clinical Pearls

- Migraine headaches can occur in children and adolescents, as well as adults.
- Most patients presenting for the evaluation of headaches do not need diagnostic testing beyond the history and physical. However, the presence of focal neurologic deficits or other red-flag symptoms/signs should prompt an immediate workup or referral.

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Case 35

A 56-year-old man comes in for a routine health maintenance visit. He is new to your practice and has no specific complaints today. He has hypertension for which he takes hydrochlorothiazide, and he occasionally takes an aspirin because someone told him that it was good for him. He has no other significant medical history. He does not smoke cigarettes, occasionally drinks alcohol, and does not exercise. His father died of a heart attack at age 60 years and his mother died at age 72 years of cancer. He has two younger sisters who are in good health. On examination, his blood pressure is 130/80 mm Hg and his pulse is 75 bpm. He is 6 ft tall and weighs 200 lb. His complete physical examination is normal. You order a fasting lipid panel, which subsequently returns with the following results: total cholesterol 242 mg/dL; triglycerides 138 mg/dL; high-density lipoprotein (HDL) cholesterol 48 mg/dL; and low-density lipoprotein (LDL) cholesterol 155 mg/dL.

- What is this patient's LDL-cholesterol goal?
- What other laboratory testing is indicated at this time?
- What is the recommended management at this point?

ANSWERS TO CASE 35:
Hyperlipidemia

Summary: A 56-year-old man with well-controlled hypertension is found to have elevated cholesterol on a screening blood test as part of a physical examination. He has no known history of coronary artery disease or of any coronary artery disease risk equivalent.

- **Goal for LDL-cholesterol:** Less than 130 mg/dL.
- **Further testing at this time:** Blood glucose, creatinine, liver function tests, thyroid-stimulating hormone.
- **Initial management of his elevated cholesterol:** Therapeutic lifestyle changes.

ANALYSIS

Objectives

1. Know the risk factors for cardiovascular disease.
2. Know the Adult Treatment Panel (ATP) III guidelines for the diagnosis, evaluation, and management of hyperlipidemia.
3. Be able to counsel patients on therapeutic lifestyle changes to lower their cholesterol levels.

Considerations

This case illustrates a 56-year-old man with well-controlled hypertension and total cholesterol 242 mg/dL; triglycerides 138 mg/dL; high-density lipoprotein (HDL) cholesterol 48 mg/dL; and low-density lipoprotein (LDL) cholesterol 155 mg/dL. The main cholesterol component that impacts on cardiovascular disease is the LDL level. Because this individual has a cardiovascular risk factor score of 2 (age and LDL), this patient's LDL goal is 130 mg/dL. Initially therapeutic lifestyle changes should be used such as weight loss, exercise, and diet, and then the fasting lipid panel should be repeated in 6 weeks. At the repeat visit, if the LDL cholesterol continues to be elevated, then discussion of pharmacologic therapy should ensue.

APPROACH TO
High Cholesterol

DEFINITIONS

ATP III: The third report of the National Cholesterol Education Program Expert Panel on the Detection, Evaluation and Treatment of High Blood Cholesterol in Adults.

HDL CHOLESTEROL: High-density lipoprotein cholesterol.

LDL CHOLESTEROL: Low-density lipoprotein cholesterol.

STATIN: Medication in the beta-hydroxy-beta-methylglutaryl-coenzyme A (HMG-CoA)-reductase inhibitor class. These are the most widely used medications for lowering LDL cholesterol.

CLINICAL APPROACH

It is important to remember that cholesterol is not a disease; however, high cholesterol is a risk factor for coronary heart disease (CHD). As such, **an individual's cholesterol levels must be interpreted in the context of their overall risks for CHD.** The recommended intensity with which we want to lower someone's cholesterol level should be proportionate to their risk of CHD: the higher one's risk, the lower the cholesterol goal. To do this, one must first learn what these major risks are.

Someone with known CHD has a greater than 20% risk of having another CHD event in 10 years. Persons with other forms of atherosclerotic disease (peripheral arterial disease, cerebrovascular disease, or abdominal aortic aneurysm), type 2 diabetes, or multiple risk factors that together raise the risk of CHD to greater than or equal to 20% in 10 years, are said to have a CHD risk equivalent. **People with known CHD or CHD risk equivalents have the highest risk of future CHD events and, therefore, their cholesterol targets are the lowest.** Similarly, someone with one or fewer risk factors for CHD is at low risk of having a CHD event. These people usually have a less than 10% risk of a CHD event in 10 years. In this population, the recommended lipid levels are not as low.

A third population is one with intermediate risk when compared to the previous two groups. They have two or more risks factors, but a CHD risk between 10% and 20%. In this population, an individual risk should be calculated. Numerous risk calculators are available online or for download into a PDA (personal digital assistant). One is available from the National Heart, Lung, and Blood institute at www.nhlbi.nih.gov/guidelines/cholesterol/index.htm. By determining the individual risk of CHD, one can then determine an appropriate lipid goal for that patient.

Determination of Lipid Goal

Numerous studies show that **LDL cholesterol is a major risk for developing CHD and that lowering LDL cholesterol can reduce this risk.** For these reasons, the ATP III guidelines focus on the identification of those with high LDL cholesterol, the determination of that individual's risk of CHD, and development of an appropriate management plan to reach LDL cholesterol goals.

These guidelines recommend measuring lipid levels in all adults older than age 20 years every 5 years. The test performed can be either a fasting lipid panel (total, LDL, and HDL cholesterol; triglycerides) or a nonfasting total and HDL cholesterol, with subsequent fasting lipid panel if either total cholesterol is over 200 mg/dL or if HDL cholesterol is less than 40 mg/dL. Table 35–1 lists the ATP III classification of lipid levels.

LDL cholesterol is the primary goal of management. Along with the presence of CHD or a CHD risk equivalent, the following **five factors are considered to determine the LDL goal** of a given individual:

Table 35–1 ATP III CLASSIFICATION OF LIPID LEVELS

LDL Cholesterol (mg/dL)	
<100	Optimal
100-129	Near optimal/above optimal
130-159	Borderline high
160-189	High
190 or greater	Very high
Total cholesterol (mg/dL)	
<200	Desirable
200-239	Borderline high
240 or greater	High
HDL cholesterol (mg/dL)	
<40	Low
60 or greater	High

Data from ATP III report.

- **Cigarette smoking**
- **Hypertension** (blood pressure ≥140/90 mm Hg or on antihypertensive medication)
- **Low HDL**
- **Age** (≥45 years for men; ≥55 years for women)
- **Family history of premature CHD** (male first-degree relative ≤55 years of age; female first-degree relative ≤65 years of age)

A high HDL level is considered a negative risk, which removes one other risk factor from the total.

The LDL cholesterol goal is based upon the evaluation of these risks. A person with **CHD or a CHD risk equivalent has an LDL goal of 100 mg/dL or less.** Someone with **zero to one identified risks has an LDL goal of 160 mg/dL or less.** An individual with two or more risks should have an individual risk assessment performed, using a risk calculator. If someone has **two or more risk factors and an individual risk of between 10% and 20%, that person's LDL goal is 130 mg/dL or less.** However, if the individual risk is greater than or equal to 20%, that person should be treated as having a CHD equivalent, with a goal LDL of less than 100 mg/dL (Table 35–2).

An update to the ATP III was issued in 2004 with an interpretation of some more recent clinical trials. This update suggests a **"therapeutic option" of a very low LDL goal of less than 70 mg/dL for those patients at very high risk of CHD.** This very-high-risk category includes people with CHD and either multiple major risk factors (especially diabetes), poorly controlled risk factors (especially smoking), multiple risk factors of metabolic syndrome (see Case 33), or an acute coronary syndrome.

Table 35–2 MANAGEMENT GUIDELINES TO REACH LDL GOALS

RISK CATEGORY	LDL GOAL	LDL LEVEL TO START THERAPEUTIC LIFESTYLE CHANGE	LDL LEVEL TO CONSIDER MEDICATION
CHD or CHD equivalent	<100	≥100	≥130 (optional for 101-129)
Two or more risks factors	<130	≥130	10-yr risk 10%-20% ≥160 10-yr risk <10% ≥190
0-1 risk factors	<160	≥160	≥190

All LDL levels in mg/dL. Data from ATP III report.

Evaluation

When high blood cholesterol is identified, an investigation should be performed to evaluate for **secondary causes of dyslipidemia.** Included among these causes are **diabetes, hypothyroidism, obstructive liver disease, and chronic renal failure.** Consequently, a reasonable laboratory workup includes fasting blood glucose, thyroid-stimulating hormone (TSH), liver enzymes, and a creatinine level. Certain medications, including progestins, anabolic steroids, and corticosteroids, also can result in elevated cholesterol. Consideration should be given to changing or discontinuing these when possible.

Management

Therapeutic lifestyle changes (TLCs) are the cornerstone of all treatments for hyperlipidemia. All patients should be educated on healthier living, including dietary modifications, increased physical activity, and smoking cessation. Weight reduction should be encouraged.

Specific dietary recommendations should include a **reduction of saturated fats to less than 7% of total calories and an intake of less than 200 mg/d of cholesterol.** Total dietary fat should be kept to no more than 35% of total calories, with less than 10% polyunsaturated fat. Trans fats should be kept as low as possible.

When dietary restriction alone does not lead to adequate LDL reduction, the addition of dietary soluble fiber and plant stanols/sterols can be beneficial. Soluble fiber 10 to 25 g and of plant stanols/sterols 2 g can be added to aid in cholesterol reduction. Referral to a dietician may be helpful as well.

When TLC is instituted, regular follow-up must be arranged. Fasting lipids should be rechecked in approximately 6 weeks. If adequate reduction has occurred, reinforcement of the lifestyle changes should be given and the patient followed every 4 to 6 months.

Pharmacotherapy may be considered in patients who do not reach their LDL goals with TLC alone. **TLC should continue to be reinforced and encouraged even when starting medications.** In someone who does not have CHD or a risk equivalent (primary prevention), medications should be considered after the third visit of TLC management. In someone with CHD or an equivalent (secondary prevention), the more stringent LDL goals often require earlier institution of drug treatment.

The first-line pharmacotherapy for LDL cholesterol reduction is a statin. **Statins not only reduce LDL cholesterol but also reduce the rates of coronary events, strokes, cardiac death, and all-cause mortality.** When statin therapy is started, fasting lipids should be rechecked in 6 weeks. If LDL goals are not met, the dose of the statin can be increased or a second agent added. These other medications include fibric acids, nicotinic acids, bile acid sequestrants, and cholesterol absorption blockers (Table 35–3). When taking statins,

Table 35–3 MEDICATIONS USED TO LOWER CHOLESTEROL

DRUG CLASS/ MEDICATION	EFFECTS	SIDE EFFECTS	CONTRAINDICATIONS
Statin • Lovastatin • Pravastatin • Fluvastatin • Atorvastatin • Cerivastatin • Simvastatin	LDL ↓ 18%-55%; HDL ↑ 5%-15%; Triglytrides (TG) ↓ 7%-30%	Myopathy, myalgia, increased liver enzymes	Active or chronic liver disease; relative contraindication with cytochrome P-450 inhibitors, cyclosporine, macrolides, antifungals
Bile acid sequestrants • Cholestyramine • Colestipol • Colesevelam	LDL ↓ 15%-30%; HDL ↑ 3%-5%; TG no change; or increase	GI distress, constipation, decreased absorption of other meds	Dysbetalipoproteinemia; TG >400
Nicotinic acids • Immediate-release, sustained-release, or extended-release nicotinic acid	LDL ↓ 5%-25%; HDL ↑ 15%-35%; TG ↓ 20%-50%	Flushing, hyperglycemia, hyperuricemia, upper GI distress, hepatotoxicity	Absolute: chronic liver disease, severe gout; relative: diabetes, hyperuricemia, peptic ulcer disease
Fibric acids • Gemfibrozil • Fenofibrate • Clofibrate	LDL ↓ 5%-20%; HDL ↑ 10%-20%; TG ↓ 20%-50%	Dyspepsia, gallstones, myopathy, unexplained non-CHD deaths in WHO study	Severe renal disease, severe hepatic disease
Cholesterol absorption blocker • Ezetimibe	LDL ↓ 13%-25%; HDL ↑ 3%-5%; TG ↓ 5%-14%	Abdominal pain, diarrhea	Hepatic insufficiency/active liver disease

Data from ATP III report and ezetimibe product information.

liver enzymes must be monitored as well (6-12 weeks after initiation or dosage change, then every 6-12 months). When goal levels are met, regular follow-up should be arranged to reinforce lifestyle changes, medication compliance, and overall risk factor reduction.

Comprehension Questions

35.1 A 62-year-old smoker with no known history of CHD presents for follow-up of intermittent claudication. He has normal blood pressure and no family history of premature CHD. His HDL cholesterol is 48 mg/dL. According to the ATP III guidelines, which of the following is his goal LDL?

A. 70 mg/dL
B. 100 mg/dL
C. 130 mg/dL
D. 160 mg/dL

35.2 A 55-year-old woman presents to your office for follow-up. She was discharged from the hospital 1 week ago following a heart attack. She has quit smoking since then and vows to stay off cigarettes forever. Her lipid levels are total cholesterol 240 mg/dL, HDL 50 mg/dL, LDL 150 mg/dL, and triglycerides 150 mg/dL. Which of the following is the most appropriate management at this time?

A. Institute therapeutic lifestyle changes alone.
B. Institute therapeutic lifestyle changes and start on a statin.
C. Start on a statin.
D. Institute therapeutic lifestyle changes and start on a statin and nicotinic acid.

35.3 A 48-year-old man with no significant medical history and no symptoms is found to have elevated cholesterol at a health screening. Which of the following tests is part of the routine evaluation of this problem?

A. ECG
B. Stress test
C. Complete blood count (CBC)
D. Thyroid-stimulating hormone (TSH)

ANSWERS

35.1 **B.** This patient has symptomatic peripheral arterial disease, which is considered a CHD risk equivalent. His LDL goal is 100 mg/dL or less.

35.2 **B.** This patient has known CHD, documented by her recent myocardial infarction. Her goal LDL is 100 mg/dL or less. As her starting level is above 130 mg/dL, it would be reasonable to start both TLC and a statin to help her to reach her goal. Nicotinic acid may be a reasonable addition if the TLC and statin do not lead to adequate LDL reduction.

35.3 **D.** Hypothyroidism is a potential cause of secondary dyslipidemia. A TSH is a reasonable test to perform in this setting. There is no indication to screen for CHD with an ECG or stress test in this asymptomatic person. Other tests to perform could include fasting blood glucose, liver enzymes, and a measurement of renal function.

Clinical Pearls

- Lipid levels must always be interpreted in the context of the individual's overall risk factors for CHD.
- Statins have the best data to support improvement in outcomes that are clinically significant, such as heart attacks, strokes, and death. Unless there is a contraindication, a statin should be the first medication used for cholesterol reduction.
- Remind patients who are taking lipid-lowering medications that lifestyle modifications are still necessary. Medications are not a substitute for a healthy lifestyle.

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Case 36

A 20-month-old girl, new to your practice, is brought in by her mother because she's been crying and not walking for the past day. Her mother reports that the child is "very clumsy and falls a lot." She says that the little girl may have injured her leg by falling off the sofa because, she repeats, "she really is clumsy and falls a lot." Upon review with the mother, she states that the child has no significant medical history and takes no medications regularly. There are two older children in the family, ages 4 and 6 years, who are in good health but also are "clumsy and forever hurting themselves." The husband lives in the home. Without any questioning or prompting, the mother states that her husband is "a good man but he's under a lot of stress." You ask the mother to undress the child for an examination and she quickly replies, "Do you really have to undress her? She's very shy." You politely, but firmly, say that you need to examine her and she removes the child's pants. You see that her right knee is visibly swollen and tender to palpation on the medial bony prominences. You also note numerous bruises of the buttocks and posterior thighs, which appear to be of different ages. There are also several small, circular scars on the legs, each about a centimeter in size. "See how clumsy she is?" the mother says, pointing to her bruises. An x-ray of the child's knee shows a corner fracture of the distal femoral metaphysis.

- What is the likely mechanism of this child's injuries?
- What further evaluation is necessary at this time?
- What legal obligation must a physician fulfill in this circumstance?

ANSWERS TO CASE 36:
Family Violence

Summary: A 20-month-old girl is brought to the office for evaluation of crying and not walking. On examination, she is found to have multiple bruises and circular wounds that are suspicious for cigarette burns. Her knee x-ray shows a metaphyseal corner fracture, an injury that is inconsistent with the stated history of "falling off the sofa."

- **Most likely mechanism of injuries:** Inflicted injuries, including leg injury from forceful pulling, bruising from hitting the child's legs, and cigarette burns.
- **Further evaluation at this time:** Complete, unclothed physical examination of child (including ophthalmoscopic and neurologic examinations); radiographic skeletal survey.
- **Legal obligation of physician:** Report of suspected child abuse to the appropriate child protective services organization.

ANALYSIS

Objectives

1. Learn the symptoms and signs suggestive of abuse.
2. Know the situations in which the risk of family violence increases.
3. Learn some of the medicolegal requirements involved in situations of family violence.

Considerations

Family violence can occur in families of any socioeconomic class and in households of any composition. The term ***family violence*** **includes child abuse, intimate partner violence, and elder abuse.** The abuse that occurs can be physical, sexual, emotional, psychological, or economic. It can take the forms of battering, raping, threatening, intimidating, isolating from friends and family, stealing, and preventing the earning of money, among many others.

In the case presented here, there are several signs of intentionally inflicted injuries to the child. The presence of numerous bruises of varying ages, especially on relatively protected areas such as the buttocks and upper posterior thighs, should raise suspicions. Finding injuries inconsistent with the reported history also can be a clue. Certain types of fractures, such as metaphyseal corner fractures (caused by forceful jerking or twisting of the leg) are usually a result of abuse. The identification of wounds consistent with cigarette burns is highly specific for abuse.

Physicians often find these situations extremely difficult and uncomfortable to deal with. They may feel caught between two partners—both of whom are patients—but who give conflicting stories. They may have concerns about the legal implications of their findings and fear legal actions if they make reports to authorities. They may have frustrations in dealing with a person who will not leave an abusive spouse and may feel ill-trained to deal with many of these situations. By knowing situations in which family violence is more likely to occur, knowing the laws regarding disclosure and reporting, and learning to recognize the signs of family violence, physicians can be better prepared to address these situations when they occur.

APPROACH TO Family Violence

DEFINITIONS

NEGLECT: Failure to provide the needs required for functioning or for the avoidance of harm.

PHYSICAL ABUSE (BATTERY): Intentional physical actions (eg, biting, kicking, punching) that can cause injury or pain to another person.

CLINICAL APPROACH

Family violence is an abuse of power, **in which a more-powerful person exerts control over a less-powerful person or persons.** This abuse can take the form of physical violence (battery), sexual violence, intimidation, emotional and psychological abuse, economic control, neglect, and isolation from others.

Intimate Partner Violence

Although intimate partner violence (IPV) is most common to think of this as a man abusing a woman, abuse can occur both in homosexual relationships and in heterosexual relationships with a male victim. It is estimated that **1 to 4 million women are abused annually in the United States and that approximately 1 in 3 women are abused at some time in their lives.**

Abuse can occur in any relationship or in any socioeconomic class. Certain situations increase the likelihood, or escalate the occurrences, of abuse. These situations include changes in family life (such as pregnancy, illnesses, deaths), economic stresses, and substance abuse. Personal and family histories of abuse also increase the likelihood of family violence. Most women do not disclose abuse to their physicians.

Numerous professional organizations, such as the American Medical Association, the American Academy of Family Physicians, and the American College of Obstetricians and Gynecologists, advocate for the routine screening of women for abuse by direct questioning. Numerous tools exist for screening, from simple questioning ("Do you feel safe in your home?") to more formal inventory tools. The United States Preventive Services Task Force (USPSTF) has found insufficient evidence to make a recommendation for or against screening for domestic violence because they did not find studies that directly looked at the impact of screening on reducing adverse outcomes. The USPSTF does recommend that **all clinicians should be alert to physical and behavioral signs and symptoms associated with abuse and neglect, and that direct questions about abuse are justifiable,** due to high levels of undetected abuse in women and the potential value of helping these patients. Recommendations regarding interactions with victims of abuse include exhibiting compassionate, nonjudgmental, supportive care in a private, secure environment.

Victims of abuse can present with varied symptoms and signs suggestive of the problem. Direct physical findings can include obvious traumatic injuries, such as contusions, fractures, "black eyes," concussions. and internal bleeding. Genital, anal, or pharyngeal trauma, sexually transmitted diseases (STDs), and unintended pregnancy may be signs of sexual assault. Depression, anxiety, panic, somatoform and posttraumatic stress disorders, and suicide attempts can also result from abusive relationships.

Some signs and symptoms may be less obvious and may require numerous encounters until the finding of family violence is made. **Victims of abuse may present to doctors frequently for health complaints or have physical symptoms that cannot otherwise be explained.** Delays in treatment for physical injuries may be a sign of IPV. Chronic pain, frequently abdominal or pelvic pain, is commonly a sign of a history of abuse. The development of substance abuse or eating disorders may prompt inquiry into family violence as well. Children of women abused often directly witness the abuse of their mother. Children and adolescents of abused women can exhibit aggression, anxiety, bedwetting, and depression.

When abuse is identified, an initial priority is to assess the safety of the home situation. Direct questioning regarding increasing levels of violence, the presence of weapons in the home, as well as the need for a plan for safety for the victim and others at home (children, elders), is critical. Resources, such as shelters, should be provided. It may be helpful to allow the patient to contact a shelter, law enforcement, family members, or friends, while still in the doctor's office. Multidisciplinary interventions, including family, medical, legal, mental health, and law enforcement, are often necessary.

The **laws regarding clinician reporting of partner violence vary from state to state.** It is important to know the statutes in your locality. Many states do not require contacting legal authorities if the victim of the abuse is a competent adult.

Child Abuse

Approximately 1 million cases of child abuse, with more than 1000 deaths, are reported each year in the United States; the number of unreported cases makes the overall prevalence much higher. The situations that increase the risk of child abuse are similar to those that increase the likelihood of other family violence. These include parental depression, substance abuse, social isolation, and increased stress. Societal factors include dangerous neighborhoods and poor access to recreational resources. Children who are chronically ill or who have physical or developmental disorders may be at even higher risk. Protective factors include family support from community or relatives, parental ability to ask for help, and access to mental health resources. Identification of at-risk families and home visitation interventions has been shown to significantly reduce child abuse. Short- and long-term physical, psychological, and social consequences are often seen in the victims of child abuse.

Certain history and physical examination findings raise the suspicion for child abuse. **Injuries that are inconsistent with the stated history or a history that repeatedly changes with questioning should raise the suspicion of abuse.** Children who are taken to numerous different physicians or emergency rooms, or who are brought in repeatedly with traumatic injuries, may be victims. Delay in seeking medical care for an injury may also be a clue to abuse.

Neglect is also a form of child abuse. An injury or illness that occurred because of lack of appropriate supervision may be a sign of neglect. Failure to provide for basic nutritional, healthcare, or safety needs may be other forms of neglect.

Children frequently have bruises, fractures, and other injuries that occur accidentally and it can be difficult to distinguish with certainty whether an injury is accidental or intentional. However, **certain types of injuries are uncommon as accidents** (Table 36–1). The presence of these injuries is highly suggestive of child abuse.

When an injury suspicious for child abuse is identified, attention should initially focus on treatment and protection from further injury. A complete examination should be performed and all injuries documented with drawings or photographs. An x-ray skeletal survey can be performed to look for evidence of current or previous bony injuries. Ophthalmologic examination should be performed to look for retinal hemorrhages. The progress note should be documented carefully and legibly.

All 50 states require reporting of suspected child abuse to the appropriate authorities (refer to local laws to determine the appropriate authority). Parents should be informed that a report is going to be made and the process that is likely to occur after the report is made. Consideration must also be given to the possibility that there are other victims of abuse in the home (spouse, other children, elders). **Any health-care provider who makes a good-faith report of suspected abuse or neglect is immune from any legal action, even if the investigation reveals that no abuse occurred.** Providers may be held liable for failure to report child abuse.

Table 36–1 INJURIES SUGGESTIVE OF CHILD ABUSE

Stocking-and-glove burns of the extremities (immersion in scalding water)
Burns of the buttock and groin that spare the intertriginous areas (immersion in scalding water)
Centimeter-sized circular burns (cigarettes)
Multiple bruises of differing ages (most common manifestation of child abuse)
Unexplained injury to buttocks, thighs, ears, neck
Bite marks
Bruises in the shape of a hand, belt buckle, or loops of a cord
Retinal hemorrhages ("shaken baby syndrome")
Corner or "bucket-handle" fractures of metaphysis of long bones
Spiral fracture of femur or humerus
Posterior rib fractures
Scapular fractures
Spinous process fractures
Sternal fractures
Complex, bilateral, or wide skull fractures
Injury to external genitalia
Sexually transmitted diseases, genital warts
Circumferential hematoma of anus (forced penetration)

Elder Abuse

Many types of elder abuse may occur, including physical, sexual, and psychological abuse, neglect, and financial exploitation. An estimated 2 million elders (3.2% of elderly) are abused in some form annually in the United States. Along with the other risks for domestic violence, several factors unique to the care of elders may play a role. The majority of abusers are family members. Caregiver frustrations and burnout are commonly heard excuses for abuse. Abusers often have histories of mental health problems or substance abuse and have little insight into the fact that they are abusing the patient. Women older than 75 years are statistically the most abused group. **Persons who are older, more cognitively and physically debilitated, and have less access to resources are more likely to be abused or exploited.**

A history of abuse may be difficult to obtain, as the patient may fear worsening of the abuse or may not have the cognitive ability to make an accurate report. If feasible, it is **helpful to interview the patient without the presence of the caregiver.** Screening the caregiver in private for stress with referral for community resources may prevent abuse in the elderly. The physical examination, like in child abuse, should carefully document any injuries that are found. Suspicions of dehydration or malnutrition should be confirmed with appropriate laboratory testing and radiographs should be performed as necessary.

By law, elder abuse should be reported to the appropriate adult protective services, but the reporting requirements vary by state. A multidisciplinary approach, involving medical providers, social workers, legal authorities, and families is usually necessary to address the issues involved.

Comprehension Questions

36.1 A 42-year-old woman presents to your office for evaluation of chronic abdominal pain. She has seen you multiple times for this complaint, but the workup has always been negative. On examination, her abdomen is soft and there are no peritoneal signs. She has no rash, but does have a purpuric lesion lateral to her left orbit. Which of the following is the best next step in management?

A. Ask the patient about physical abuse and report suspicions to the local police.
B. Ask the patient about physical abuse and provide information about local support services.
C. Exclude a bleeding diathesis before inquiring about abuse.
D. Order an abdominal X-ray.
E. Refer to psychiatry.

36.2 A 7-month-old boy presents to the ED with his father after a 1-day history of intractable vomiting. On examination, the child is lethargic. The anterior fontanel is closed. An abdominal x-ray shows a non-specific bowel gas pattern and incidentally reveals a mid-shaft fracture of the right femur. When confronted about the fracture, the father states that the child climbed onto a chair and jumped off yesterday. Which of the following is the most appropriate next step in management?

A. Radiographic bone survey
B. Consulting a child abuse specialist
C. Social services consult
D. Disclosing to the parent the intention of contacting child protection services
E. Non-contrast CT of the head

36.3 Which of the following injuries is most likely to be caused by abuse of a toddler?

A. Three or four bruises on the shins and knees
B. Spiral fracture of the tibia
C. A displaced posterior rib fracture
D. A forehead laceration

36.4 An 80-year-old man, who resides in a local nursing home is seen in your office for unexplained scratches on arms, and bandlike bruises on wrists and ankles consistent with restraint use. The patient is mildly demented, and appears scared. There is no family to contact. Examination and laboratory results show no medical reason for easy bruising. Which of the following should be your next step?

A. Refer to nursing home social worker.
B. Contact nursing home ombudsmen program.
C. Have the patient observed by nursing home staff.
D. Contact nursing home vice president for nursing care.
E. Send the patient back to the nursing home.

ANSWERS

36.1 **B.** It is appropriate to discuss your concerns in a nonaccusatory, nonjudgmental fashion with your patient. Waiting for her to bring up the subject may result in her suffering further abuse. The reporting of the abuse of competent adults (not elders) is not mandated by law in most states. You should offer assistance, evaluate her safety, and provide her with information regarding available services in the area. There is no reason to exclude a bleeding diathesis before approaching the subject of abuse.

36.2 **E.** This child has injuries consistent with physical abuse. In children less than 1 year of age, 75% of fractures are due to abuse. Moreover, the shape of a fracture—spiral, transverse, etc.—is less important in suspected abuse than the age of the child and location of the fracture. The purported history of fall is inconsistent with the developmental abilities of a 7-month old child. The child has intractable vomiting and is lethargic on examination. These findings are worrisome for neurologic damage. A CT should be ordered to exclude intracranial bleed, since this disorder may lead to irreversible brain damage or even death if not identified quickly. While a radiographic bone survey is indicated in all children less than 2 years of age with suspected abuse, it should be done after excluding more urgent conditions. Providers have a responsibility to notify the appropriate authorities when abuse is suspected; however, it is inadvisable to disclose this intention to the parent. Lastly, the anterior fontanel closes between 4-26 months of age (avg. 13.8 months). It may bulge in conditions, such as meningitis or intracranial hemorrhage, which increase intracranial pressure.

36.3 **C.** A posterior rib fracture is often the result of grabbing and squeezing the chest violently. It is very suspicious for abuse. A spiral fracture of the tibia is known as a "toddler's fracture" and is a common injury that is often confused with abuse, but not often caused by abuse. Bruises on the anterior and over bony prominences such as the shins, knees, and forehead injuries are common from falls while learning to walk. Well-padded areas that are bruised such as the thigh, buttock, and cheeks increase likelihood of abuse.

36.4 **B.** Clinicians have a legal duty to report possible elder to abuse to adult protective services in their community. If the patient is living in a nursing care facility, each state has nursing home ombudsmen who can investigate. The Ombudsmen Program is mandated by the Federal Older Americans Act. If you feel that this patient is in immediate danger, he can be admitted for evaluation of bruising while the ombudsmen and local adult protective services investigate for substandard care or abuse at the nursing care facility.

Clinical Pearls

- Suspected child and elder abuse must be reported. Good-faith reports of suspected abuse are a shield to lawsuits; failure to report can result in legal action against the physician.
- When seeing a suspected abuse victim, always consider the possibility that there could be other abuse victims in the household.

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Case 37

A 12-year-old boy is brought to the physician's office with right thigh pain and a limp. His mother has noticed him limping for the past week or so. He denies any injury to his leg but says that it hurts some when he plays basketball with his friends. He denies back pain, hip pain, or ankle pain. He occasionally gets some pain in the right knee but does not have any swelling or bruising. He has no significant medical history, does not take any medications regularly, and otherwise feels fine. On examination, he is an overweight adolescent. His vital signs and a general physical examination are normal. When you have him walk, he has a prominent limp. You note that he seems to keep his weight on his left leg for a greater proportion of his gait cycle than he does on the right leg. Examination of his back reveals a full range of motion, no tenderness, and no muscle spasm. He gets pain in the right hip when it is passively internally rotated. When the hip is passively flexed there is a noticeable external rotation. There is no thigh muscle atrophy. His right knee and the remainder of his orthopedic examination are normal.

- What is the most appropriate test to order first for this patient?
- What is the most likely diagnosis?
- What complication could occur if this problem is not diagnosed and treated?

ANSWERS TO CASE 37:
Limping in Children

Summary: An overweight 12-year-old boy presents for evaluation of a limp and thigh pain. There is no history of injury or trauma. He is found to have pain on internal rotation of the hip and his hip externally rotates when passively flexed. He bears weight more on his left leg than his right while walking.

- **Most appropriate test to order:** X-ray of the right hip.
- **Most likely diagnosis:** Slipped capital femoral epiphysis.
- **Complication for which he is at risk:** Avascular necrosis of the hip.

ANALYSIS

Objectives

1. Develop a differential diagnosis of the most likely causes of leg pain and limping in children.
2. Know common causes of leg pain and limping in children of different ages.
3. Know appropriate examination, laboratory, and radiologic evaluation for the limping child.

Considerations

Leg pain is a common complaint in childhood. The most common causes of leg pain in children are acute injuries—sprains, strains, contusions, and so on. However, leg pain and limping can be a sign of a more serious, even life-threatening, pathology. Learning an approach to the evaluation and the common diagnoses involved may help in the identification of these problems earlier, when a better outcome is more likely.

To understand a limp, it is first important to understand the normal gait. Gait is composed of two phases: the "swing" and the "stance" phases. The stance phase is the weight-bearing phase and accounts for approximately 60% of the gait cycle. The swing phase is the non–weight-bearing phase, when the foot lifts off the ground and is propelled forward. The **antalgic gait occurs when the stance phase of gait is shortened, usually because of pain during weight bearing.** Antalgic gait is the most common type of limp and is the type of gait described in this case.

There are many causes of limp with pain in children; some of the more common causes may be broadly categorized as being primarily orthopedic, reactive, infectious, rheumatologic, or neoplastic. The prevalence of the specific diagnoses also varies by age. Limp without pain is usually due to congenital orthopedic anomalies or neuromuscular disorders.

In the specific case presented, there are several symptoms and signs that make the diagnosis of slipped capital femoral epiphysis (SCFE) likely. The absence of a specific injury is significant, as SCFE is the most common nontraumatic hip pathology in adolescents. The initial complaint of thigh pain may lead to other considerations, but **hip pathology will frequently present with pain in the groin, thigh, or even the knee.** The patient's age and body habitus are typical for SCFE, which is classically described as occurring most often in overweight adolescent males. Pain with internal rotation of the hip and the finding of external rotation on passive flexion of the affected hip are also suggestive of SCFE.

APPROACH TO
Limping With Pain in Children

DEFINITIONS

AVASCULAR NECROSIS: Death of living bone tissue caused by disruption of blood flow.

DYSPLASIA: Abnormal growth or development.

CLINICAL APPROACH

One of the key characteristics of the evaluation of the child with a limp is assessing whether there is pain or no pain. In an antalgic gait, the cause of the pain may range from the back to the foot (see Table 37–1). Therefore, unless there is an obvious source of pain, the examination should include assessment of the back, pelvis, buttock, leg, and foot. In the child who clings to the parent, separating the child from the parent will allow the clinician to observe the child's gait when they walk back to the parent. The child who walks stiffly may be avoiding moving the spine indicating a possible discitis. Those with inflammation or muscle weakness in the hip will move the torso over the pathologic side (Trendelenburg gait). Inspecting the feet may show clawing of the toes or cavus deformity, which are signs of neuromuscular conditions.

Because hip pathology often presents with vague pain and hip conditions are likely to need emergent treatment, evaluation of the hip may be the most important part of the examination of a patient in whom the site of pathology is not immediately obvious. Internal rotation of the hip increases the intracapsular pressure within the acetabulum. Pain during a leg roll (supine child with extended hip and knee; one examiner stabilizes the pelvis while another rolls leg internally and externally) and limited internal rotation of less than 30 degrees may indicate infectious or orthopedic hip pathology. The FABER test (*F*lexion, *Ab*duction, *E*xternal *R*otation—the ipsilateral ankle placed on

Table 37–1 COMMON CAUSES OF LIMP WITH PAIN IN CHILDREN

Orthopedic
- Fracture
- Stress fracture
- Pathologic fracture through tumor or cyst
- Sprain/strain/contusion
- Slipped capital femoral epiphysis
- Early Legg-Calvé-Perthes disease

Reactive
- Toxic synovitis
- Transient synovitis following viral infection
- Rheumatic fever

Infectious
- Septic arthritis
- Osteomyelitis
- Cellulitis
- Discitis
- Gonococcal arthritis

Rheumatologic
- Juvenile rheumatoid arthritis
- Systemic lupus erythematosus

Tumor
- Benign tumors (osteoid osteoma, osteoblastoma)
- Ewing's sarcoma
- Osteosarcoma

Other
- "Growing pains"

the contralateral knee and mild downward pressure placed on the ipsilateral knee) can find pathology located in the sacroiliac joint, often seen in rheumatologic disorders.

X-rays should be obtained when the differential indicates a likelihood of bony abnormalities. In nonverbal children, x-rays from hip to feet can find a fracture in a significant minority of children with limp. A complete blood count should be drawn if there is concern of an infectious cause. An erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) should be considered in evaluating infectious and rheumatologic etiologies. Consider Lyme disease in endemic areas, as this can mimic both infectious and rheumatologic causes of hip disorders. Any joint where septic arthritis is considered should have a joint aspiration and evaluation of synovial fluid. Fever greater than 99.5°F and ESR greater than 20 is 97% sensitive for septic hip joint. Testing of the fluid should include culture for gonorrhea in teens who are sexually active.

The evaluation of limping without pain (Table 37–2) should include measurements for leg length discrepancies (measure umbilicus to medial malleolus)

Table 37–2 COMMON ORTHOPEDIC CAUSES OF LIMP WITHOUT PAIN IN CHILDREN

Congential developmental dislocation of hip
Spastic hemiplegia (cerebral palsy)
Legg-Calve-Perthes (subacute and chronic)
Leg-length discrepancy
Proximal focal femoral dysplasia
Congenital short femur
Congenital bowing of the tibia"

Data from Hollister JR. Rheumatic diseases. In: Hay WW, Levin MJ, Sondheimer JM, et al. (eds). *Current Pediatric Diagnosis and Treatment*. 15th ed. New York, NY: McGraw-Hill; 2001:734; and Leet AI, Skaggs DL. Evalution of the acutely limping child. *Am Fam Physician*. 2000;61: 1011-1018; *Rudolph's Pediatrics*. 21st ed. 2003; Chapter 27.

and observation for muscular atrophy or limb deformity. Barlow (hip and knee flexed 90 degrees, hold the knee and attempt to displace the thigh posterior), Ortolani (guided abduction), and Galeazzi (knee height discrepancy when patient lies supine with ankles to buttocks and hips and knees flexed) tests can be used to assess for congenital hip abnormalities and femoral length discrepancies.

Infants and Toddlers

Common causes of limping in children in this age group are septic arthritis, fractures, and complications of congenital hip dysplasia. **Septic arthritis** is usually monoarticular and associated with systemic signs such as fever. In young infants, the symptoms may be less obvious, such as crying, irritability, and poor feeding. Children who are ambulatory (crawlers or walkers) will often refuse to do anything that puts weight on the affected joint because of pain. Infection of a joint causes a septic effusion, which raises the pressure inside of the joint capsule. **Children with a septic hip joint will often lay with their hip flexed, abducted, and externally rotated,** which helps to reduce the pain, and they will have significant pain with any internal rotation or extension of the joint. Children with a septic joint will usually have an elevated white blood cell count, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). Definitive diagnosis comes from joint aspiration. **Any suspected septic joint must be aspirated.** In younger infants (4 months or younger), group B streptococcus and *Staphylococcus aureus* are the most common pathogens involved. In older infants and children under the age of 5 years, *S aureus* and *Streptococcus pyogenes* are the usual causes. Treatment is urgent surgical irrigation and debridement, along with antibiotics.

Unsuspected **fractures**—either stress fractures or traumatic fractures—can present with pain and limping. Abuse must be suspected if the injury is inconsistent with the history presented, if the history changes with repeated questioning, if the child is said to have performed an act outside of his developmental ability, or if a fracture usually associated with abuse is found (see Case 36). However, the **history may not reveal the source of the injury,** as a child may fall outside of the view of the parent. **A traumatic injury may not result in limping or in complete immobility, but may cause a change in how the child ambulates.** For example, a child who previously walked and now refuses to walk but will crawl, may have an injury of the lower leg or foot.

A **toddler's fracture** is one example of an unsuspected fracture that may present primarily as a limp or a refusal to walk. This fracture is a **spiral fracture of the tibia that results from twisting while the foot is planted.** The diagnosis may be suspected in the setting of an acute limp or change in ambulation, a normal examination of the knee and upper leg and tenderness of the tibia. It can be confirmed with a plain film x-ray. Undiagnosed **congenital dysplasia of the hip may present as a painless limp that is present from the time that the child learns to walk.** All newborns and infants should have their hips examined for instability or dislocation. If undiagnosed, contractures may form that limit movement of the hip. When the child learns to walk, the child will have a painless limp. The diagnosis may be confirmed by x-rays showing abnormal hip alignment. If the problem is found in the first few weeks of life, the child can be treated with splinting of the hip and normal development usually follows. If diagnosed late, the treatment is often surgical.

Young Children

Transient synovitis is a self-limited inflammatory response that is a common cause of hip pain in children. It occurs typically in children ages 3 to 10 years, is more common in boys than in girls, and **often follows a viral infection.** It is frequently seen as gradually increasing hip pain that results in a limp or refusal to walk. These children have a low-grade or no fever, a normal white blood cell (WBC) count, and a normal ESR. On examination, there is pain with internal rotation of the hip and the overall range of motion is limited by pain. X-rays are either normal or show some nonspecific swelling. In a situation where the patient is afebrile, has pain-free rotation of hip greater than 30 degree, has a normal WBC count, normal ESR, and short-term follow-up can be assured, the patient can be followed clinically and should improve in a few days. If these conditions are not met and the diagnosis of a septic joint is considered, or if a patient followed expectantly continues to worsen, an aspiration should be done. **A septic joint will have a purulent aspirate with a WBC count greater than 50,000/μL; transient synovitis will have a yellow/clear aspirate with a lower WBC count (<10,000/μL).**

Legg-Calvé-Perthes (LCP) disease is an **avascular necrosis of the femoral head** that typically occurs in children ages 4 to 8 years. It is much more common in boys than in girls. Any disruption of blood flow to the femoral capital epiphysis, such as trauma or infection, may cause avascular necrosis. In LCP disease, the etiology of the disruption of blood flow is unknown. Children typically have a gradual onset of hip, thigh, or knee pain, and limping over a few months. Early in the course, x-rays of the hip may appear normal. Later radiographic findings include collapse, flattening, and widening of the femoral head. Bone scans or magnetic resonance imaging (MRI) may be necessary to confirm the diagnosis. The **treatment is usually conservative,** with protection of the joint and efforts to maintain range of motion. Children who develop more severe necrosis or who develop the disease at older ages may have a worse outcome and a higher risk of developing degenerative arthritis.

Adolescents

The capital femoral epiphysis is the growth plate that connects the metaphysis (femoral head) to the diaphysis (shaft of the femur). A **slipped capital femoral epiphysis** is a separation of this growth plate, which results in the femoral head being medially and posteriorly displaced. This may be caused by an acute injury, but more often is not. It is most often seen in overweight adolescent boys and presents as pain in the hip, thigh, or knee along with a limp. Examination reveals **limited internal rotation** and obligate **external rotation when the hip is passively flexed.** Early x-rays may show only widening of the epiphysis; later x-rays can show the slippage of the femoral head in relation to the femoral neck. The treatment is surgical pinning of the femoral head. These patients must be closely followed, as approximately 33% will develop avascular necrosis and 33% will develop SCFE in the contralateral hip.

Other causes of limb pain are common in adolescents. Sprains, strains, and overuse injuries are the most common cause of limb pain in this population, and are usually readily diagnosed on history and examination (see Case 12). Sexually active adolescents or teens are at risk for sexually transmitted diseases (STDs) and their complications, including gonococcal arthritis. In this population, an appropriate history, sexual history, and review of systems are necessary.

All Ages

Septic arthritis, fractures, neuromuscular disorders, and neoplasms can cause a limp in children of all ages. Pain that wakens the child at night is suspicious for malignancy. "Growing pains" is a diagnosis of exclusion. It should be considered if the pain is only at night, is bilateral, is not present during the day, and if no other pathology is found.

Comprehension Questions

37.1 A 6-year-old boy is brought in for evaluation of a painful hip. He has been limping and not wanting to walk for the past 2 days. He has had no obvious injury. He feels a little better if he is given some ibuprofen. He has not had a fever and does not have any other current symptoms, although he had "the flu" last week. On examination, his vital signs are normal. His right hip has some pain with internal rotation. He walks with a pronounced limp. Which of the following statements is most appropriate?

A. He can be sent home with a prescription for ibuprofen.
B. He should have a complete blood count (CBC) and ESR.
C. He should have an aspiration of his hip in the office.
D. If he has a normal x-ray, no further workup is needed.

37.2 An 18-month-old African American girl is brought into your office because she has been crying and stopped walking today. She will crawl, however. Her mother denies any injury to the child. On examination, she is crying but consolable in her mother's arms. She has bruising and swelling just proximal to the left ankle. An x-ray reveals a spiral fracture of the tibia. Which of the following best describes your advice to the mother of the patient?

A. You are going to report this to child protective services as suspected abuse.
B. You are going to refer the child for a bone biopsy because this is a pathologic fracture that may represent a neoplasm.
C. This is a common fracture resulting from twisting on a planted foot.
D. You should draw blood to evaluate for sickle cell disease, which may cause infarction of the bone.

37.3 A 2-year-old boy is brought in with fever and poor feeding. He started getting sick yesterday and has worsened significantly today. He has had no recent illnesses or injuries, and no known ill contacts. On examination, his temperature is 101°F (38.3°C), he is tachycardic, and he appears ill. He is lying on his back with his left leg flexed and abducted at the hip. A head, ears, eyes, nose, and throat (HEENT) examination is normal, the heart is tachycardic but regular, and the lungs are clear. The abdomen is nontender and has normal bowel sounds. He screams in pain when you move his left leg from its resting position. Blood work reveals an elevated WBC count of 15,000 mm^3 and an ESR of 45 mm/h (normal: 0-10). An x-ray of his left hip shows a widened joint space but no fractures. Which of the following is your next step at this point?

A. Oral antibiotic and follow-up in 1 day.
B. MRI of the hip and referral to an orthopedist.
C. Anti-inflammatory medication and close follow-up.
D. Hip joint aspiration.

37.4 A 6-year-old boy appears in the office with a 2-month history of slight limp. He has no significant past medical history and takes no medications. He has normal vital signs and is noted to have antalgic gait and decreased range of motion in the left hip (internal rotation more limited). He has mild pain on palpation of the anterior capsule on the left side. X-ray shows fragmentation of the femoral head. Which of the following is the most likely diagnosis?

A. Toxic synovitis of hip
B. Avascular necrosis of hip (Legg-Calvé-Perthes)
C. Slipped capital femoral epiphysis
D. Femoral shaft fracture

ANSWERS

37.1 **B.** The case presented is suspicious for transient synovitis following a viral illness. A CBC and ESR should be drawn. With a normal CBC and ESR, and if follow-up can be assured, this child could be treated expectantly, given an oral nonsteroidal anti-inflammatory drug (NSAID) with the expectation of a recovery in a few days.

37.2 **C.** The case presented is classic for a toddler's fracture. Spiral fractures of other long bones (femur, humerus) are more suspicious for abuse. Orthopedic referral is appropriate for management, but a bone biopsy or further workup is not necessary at this time.

37.3 **D.** The child in this case has all of the symptoms and signs of a septic hip joint. This situation demands a joint aspiration to confirm the diagnosis. If it is confirmed, he should be promptly referred for urgent surgical management.

37.4 **B.** This child is in the correct gender and age group with signs, symptoms, and radiologic findings associated with Legg-Calve'-Perthes disease. It is often a self-healing disorder. Treatment is focused on limiting pain and avoiding functional loss. Depending on severity and age, treatment may include watchful waiting, physical therapy, casting, and surgery

Clinical Pearls

- Hip pathology may not cause hip pain; it may cause groin, thigh, or knee pain instead.
- Because of the high risk of bilateral disease, follow-up in SCFE cases should include examination and x-rays of the unaffected hip until the growth plate closes.

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Case 38

On the third postoperative day following an uneventful open appendectomy under spinal anesthesia, a 70-year-old man with history of hypertension and benign prostatic hyperplasia (BPH) suddenly developed a temperature of 102.5°F (39.1°C) accompanied by chills and vomiting. Just before surgery, a urethral catheter was placed, which was removed 24 hours later, only to be replaced when he was unable to urinate on his own on the second postoperative day. Physical examination is unremarkable except for costovertebral angle tenderness and suprapubic tenderness. He has no abdominal guarding or rebound tenderness.

- What is the most likely cause of postoperative fever?
- What is the next diagnostic step?
- What is the most appropriate treatment at this time?

ANSWERS TO CASE 38:
Postoperative Fever

Summary: A 70-year-old man with history of hypertension and BPH who underwent open appendectomy under spinal anesthesia develops fever, chills, and vomiting on the third postoperative day. Physical examination shows costovertebral tenderness and suprapubic tenderness. He has a urethral catheter in place because of a problem in voiding.

- **Most likely cause of postoperative fever:** Urinary tract infection (UTI).
- **The next diagnostic step:** Urinalysis and urine culture.
- **Treatment:** IV antibiotic.

ANALYSIS

Objectives

1. Identify the different causes of postoperative fever based on the timing of onset, nature of surgery, and patient's risk factors.
2. Understand the different clinical presentations that point to the etiology of postoperative fever.

Considerations

This 70-year-old man with history of hypertension and BPH is at high risk for UTI because he recently underwent a pelvic procedure under spinal anesthesia and because he has urinary retention secondary to BPH. In addition, the use of a urethral catheter poses an additional risk for bacterial seeding of the urinary bladder. Suprapubic pain and costovertebral tenderness are physical findings suggestive of UTI, most likely acute pyelonephritis. For those without a urethral catheter, symptoms such as dysuria, urgency, and frequency are common. UTI is high on the list of causes of fever in the third postoperative day, although it could also occur anytime during the postoperative period. Urinalysis may detect presence of bacteriuria, pyuria, nitrites, and leukocyte esterase. Urine culture would determine the type of offending organism, the most common of which are *Escherichia coli*, *Proteus*, *Klebsiella*, *Staphylococcus epidermidis*, *Pseudomonas*, and *Candida*. In this patient, the urethral catheter needs to be changed now and discontinued as soon as he is able to void on his own. Symptomatic patients and those who are at high risk for infection are

usually treated with appropriate IV antibiotics according to the most likely pathogens. The antibiotics subsequently can be adjusted based on culture results. Blood cultures should be ordered if urosepsis is suspected. Most importantly, it is crucial to address and treat the cause of urinary retention (eg, BPH, kidney stone) to prevent recurrence and avoid complications.

APPROACH TO
Postoperative Fever

DEFINITIONS

DRUG FEVER: Fever that coincides with the administration of a particular drug and cannot otherwise be explained by clinical and laboratory findings. Resolution of the fever occurs with discontinuation of the suspected drug. Drugs that are usually implicated are β-lactams, sulfa derivatives, heparin, and amphotericin B.

MALIGNANT HYPERTHERMIA: A rare autosomal dominant disorder characterized by fever of greater than 104°F (40°C), tachycardia, metabolic acidosis, and calcium accumulation in skeletal muscle leading to rigidity. This may occur up to 24 hours after exposure to certain anesthetic agents such as halothane and succinylcholine. Treatment includes supportive therapy, such as antipyretics, oxygen, cooling blankets, and dantrolene IV.

SURGICAL SITE INFECTION (SSI): A concept introduced by the Centers for Disease Control and Prevention (CDC) and various consensus panels to replace the term surgical wound infection. This refers to any infection that occurs in the site of surgery and classified as superficial, deep, or organ/space SSI.

CLINICAL APPROACH

Fever (defined as >38.3°C/101.0°F) is the most common postoperative complication, occurring in 50% of major surgery in the immediate postoperative period. **As an integral part of informed consent prior to surgery, patients need to be made aware by the physician of the possibility of experiencing postoperative febrile episodes.** In addition, adequate preoperative evaluation, which includes performing a history and physical examination to identify risk factors, medications, nutritional status, and comorbid conditions, is imperative to avoid possible life-threatening situations during the perioperative period. Preoperative and perioperative strategies can be used to reduce the risk of developing a postoperative fever (Table 38–1). Fortunately, postoperative fever typically resolves spontaneously and most of the time does not necessarily indicate the presence of infection.

Table 38–1 STRATEGIES TO REDUCE THE RISK OF POSTOPERATIVE FEVER

Preoperative Interventions
- Optimize nutritional status
- Smoking cessation
- Treat any existing active infections
- Optimize management of existing medical conditions (eg, diabetes)
- Reduce dosage of immunosuppressive therapies (when indicated)

Perioperative Interventions
- Administer perioperative antibiotics
- Use noninvasive ventilation
- If intubation necessary, use pneumonia prevention protocols
- Remove catheters, IV lines, tubes, and drains as soon as safe
- Change lines after 72-96 hours if they are still needed
- DVT prophylaxis using early mobilization, sequential compression devices, subcutaneous heparin, or low molecular weight heparin

The etiology of postoperative fever could be infectious or noninfectious (Tables 38–2 and 38–3). The mnemonic **"5 Ws"** helps in remembering the most common causes of postoperative fever in roughly the order of frequency: **wind** (pneumonia), **water** (UTI), **wound** (SSI), **walk** (deep venous thrombosis [DVT]), and **wonder drugs** (drug fever). When a surgical patient develops fever, the differential diagnosis and investigative methods are directed by the timing of the fever, the type of surgery performed, the preexisting clinical conditions, and the presenting symptoms. A thorough physical examination should be initiated, followed by inspection of the surgical site, review of all medications, and request for necessary laboratory tests. If three or more of the following risk factors are present, the likelihood of infection as the source of fever approaches 100%.

- Preoperative trauma
- American Society of Anesthesiologists (ASA) score greater than 2 (patient with mild systemic disease or worse)
- Onset on the second postoperative day
- White blood cell (WBC) count greater than 10,000 cells/mm^3
- Blood urea nitrogen (BUN) greater than 15 mg/dL
- Systemic manifestations such as chills and rigors

Tissue trauma during surgery stimulates an inflammatory response that leads to release of pyrogenic cytokines (eg, interleukins, tumor necrosis factor, interferon) from the tissues. Elevated levels of bacterial endotoxins and exotoxins that are released from the colon as a result of surgical complications also elicit the same inflammatory response. This reaction leads to elevation of the thermoregulatory set point and production of fever (temperature >100.5°F [38°C]).

Table 38–2 COMMON CAUSES OF POSTOPERATIVE FEVER

APPROXIMATE ONSET OF FEVER	INFECTIOUS	NONINFECTIOUS
Intraoperative up to 24 hours after surgery	Preexisting infection Bacteremia from urologic instrumentation Intraperitoneal leak (up to 36 hours) Invasive soft-tissue infection Toxic shock syndrome	Surgical trauma Medications Blood products (at time of transfusion) Malignant hyperthermia
1 day to 1 week from surgery	UTI Pneumonia SSI Catheter-related infection Preexisting infection Cellulitis	Acute myocardial infarction Alcohol/drug withdrawal Gout Pancreatitis Pulmonary embolism Superficial vein thrombophlebitis (often at IV site) Benign postoperative fever (diagnosis of exclusion)
1 to 4 weeks after surgery	SSI Thrombophlebitis Pseudomembranous colitis Catheter-related infection Device-related infections Abscess	Medication toxicity DVT Pulmonary embolism
More than 1 month after surgery	Blood-transfusion hepatitis Infective endocarditis SSI Device-related infections Vascular graft infection	Postpericardiotomy syndrome

This explains why suppression of cytokine release by NSAIDs or steroids or the use of acetaminophen may alleviate fever and enhance patient comfort.

There are very **few causes of fever in the immediate postoperative period.** One of them is **malignant hyperthermia,** which is characterized by markedly elevated temperature, up to 104°F (40°C), shortly after induction of anesthesia with agents such as halothane and succinylcholine. Another cause of

Table 38–3 OTHER CAUSES OF POSTOPERATIVE FEVER WITH VARIABLE TIMING OF ONSET

INFECTIOUS	NONINFECTIOUS
Abscess	Withdrawal reaction from drugs/alcohol
Sinusitis	Subarachnoid hemorrhage
Otitis media	Bowel infarction
Parotitis	Pancreatitis
Meningitis	Hyperthyroidism
Acalculous cholecystitis	Dehydration
Osteomyelitis	Acute hepatic necrosis
Bacteremia	Hypoadrenalism
Empyema	Neoplastic fever
Fungal sepsis	Suture reaction
Hepatitis	Systemic inflammatory response syndrome (SIRS)
Decubitus ulcers	Pheochromocytoma
Perineal infections	Lymphoma
Peritonitis	Hematoma
Pharyngitis	Seroma
Tracheobronchitis	Myocardial infarction
	Gout/pseudogout
	Organ transplant-related infection
	Neuroleptic malignant syndrome

immediate postoperative fever is **bacteremia,** which occurs more commonly in urologic procedures that involve instrumentation, for example, transurethral resection of the prostate. Gram-negative bacteria are the most common pathogen. Within 30 to 45 minutes, the patient develops chills and temperature that could exceed 104°F (40°C). Accompanying symptoms such as tachycardia, tachypnea, oliguria, and hypotension are common.

If fever occurs within 36 hours post-laparotomy, there are two important infectious etiologies to be kept in mind—**bowel injury with leakage of gastrointestinal contents into the peritoneum** and **invasive soft-tissue wound infection** caused by *β-hemolytic streptococci* or *Clostridium* species. The former is accompanied by hemodynamic instability. Least common in this setting is **toxic shock syndrome** caused by *Staphylococcus aureus*.

Within the first 48 to 72 postoperative hours, **atelectasis** (partial collapse of peripheral alveoli) causes 90% of pulmonary complications of surgery. Contrary to popular beliefs, recent literature disputes its association with fever and found their coexistence to be merely coincidental. The alveolar collapse is compounded by the loss of functional residual capacity in almost all patients, and 50% reduction of vital capacity intraoperatively. Chest x-ray may reveal discoid infiltrate and an elevated hemidiaphragm. Certain conditions make

atelectasis more likely, including heavy cigarette smoking, prior lung resection, old age, malnutrition, asthma, chronic obstructive pulmonary disease (COPD), prolonged procedure, abdominal distension, and thoracic or abdominal incision.

The use of narcotics and anesthesia could also affect the patient's breathing pattern. Instructing the patient on deep inspiration and coughing, the use of incentive spirometry, and the provision of adequate pain control can facilitate the opening of the alveoli.

Without resolution of atelectasis, **pneumonia** may ensue, on the third postoperative day, when the build up of secretions facilitates growth of bacteria. Patients who are on mechanical ventilators are at highest risk for pneumonia (ventilator-associated pneumonia). Fever associated with productive cough, pulmonary crackles, elevation of WBCs, positive sputum culture, and infiltrates in chest x-ray are the usual indicators of pulmonary infection. Appropriate use of broad-spectrum IV antibiotic therapy is the treatment. **Aspiration** as the possible cause of pneumonia should be suspected in the elderly, those who reside in a nursing home, and those with neurologic dysphagia, altered mentation, and gastroesophageal reflux disease (GERD). **Gram-negative coverage is required for aspiration pneumonia,** with the current agents of choice being piperacillin/tazobactam or ticarcillin/clavulanate. It is also around this time that **UTI** should be entertained as part of differential diagnosis. UTIs can be treated with similar agents or with a fluoroquinolone.

The patient with persistent fever 5 to 7 days after surgery needs to have a thorough examination of the operative site to check for signs of infection, which include erythema, pain, local edema, and purulent discharge. **Surgical site infection** has markedly decreased through wide practice of aseptic technique. Patients at high risk of wound infection are those who underwent lengthy surgical procedure, who received blood transfusion, those who are malnourished, and those who have diabetes mellitus. Skin site infections may be treated with oxacillin or with vancomycin if methicillin-resistant *Staphylococcus aureus* (MRSA) is common in the institution or environment. Deep abdominal infections are often treated with a cephalosporin, such as cefoxitin, or a combination of fluoroquinolone plus metronidazole to cover anaerobic infections.

Drug fevers are often associated with rash and/or lupus-like syndromes. They also may have renal, liver, or hematologic dysfunction associated with the drug toxicity. Common medications associated with drug fever include cephalosporins, fluoroquinolones, sulfonamides, and penicillins.

Purulent drainage and fluctuance indicate the presence of abscess, which requires incision and drainage. When cellulitis is confirmed, treatment with antibiotic is warranted. Gram-positive bacteria, such as *S aureus, S epidermidis* (especially with implants or devices), *Streptococcus pyogenes,* and *Enterococcus,* are important pathogens. Fungal etiology should not be ruled out in patients with severe comorbid conditions. On rare occasions, deep abscesses produce fever 10 to 15 days after surgery. A high level of suspicion leads to diagnostic imaging such as computed tomography (CT) scan of the body region most

likely to be infected, which depends on the location of the surgery. Interventional radiology specialists could be called upon for radiologically guided drainage of the abscess, which is the definitive treatment. Antibiotics should include coverage for Gram-negative enteric bacilli and anaerobes. Gallium scans may be helpful in finding sites of infection in patients without localizing symptoms and workup.

Intravascular catheter or line-associated infection needs to be entertained when the patient has had IV devices for 3 days or more, even when the site appears clean. Any unnecessary lines should be discontinued, as they are potential sites of infection. The catheter tip is cultured to reveal the offending organism that would direct treatment.

Fever caused by **deep venous thrombosis** usually occurs on the fifth postoperative day. Half of the time patients with DVT are asymptomatic. Common complaints are leg edema, tenderness, pain, and warmth. **Homan sign** (pain in the calf on foot dorsiflexion) is demonstrated in some cases. When possible, surgical patients are encouraged to ambulate early; otherwise, compression devices and subcutaneous heparin or low-molecular-weight heparin are useful prophylactic measures. Diagnosis is made by duplex ultrasound, but most accurately confirmed with venography. Patients who develop **pulmonary embolism** usually have concomitant DVT. The treatment of DVT and pulmonary embolism is initiated with low-molecular-weight heparin or unfractionated heparin, followed by warfarin.

The type of surgery also provides a clue as to the associated risks of fever-associated surgical morbidity. In general, laparoscopic surgery comparatively causes fewer cases of fever than open surgery. Pleural effusion develops in all patients undergoing cardiothoracic surgery and 5% of those patients acquire pneumonia. Particularly unique to abdominal surgery is deep abdominal abscess and pancreatitis. Obstetric and gynecologic surgery could be complicated by postpartum endometritis, deep pelvic abscess, and pelvic thrombophlebitis. SSI is the most common infectious cause of fever in orthopedic surgery. Prostatic and perinephric abscess are more commonly seen in urologic procedures. Patients undergoing genitourinary procedure are at greater risk of having UTI. Meningitis is a common cause of fever following a neurosurgical procedure. Neurosurgery patients, who are usually immobilized and less aggressively anticoagulated to avoid brain hemorrhage, have the highest incidence of DVT.

Comprehension Questions

38.1 A 60-year-old man with adenocarcinoma of the colon underwent left hemicolectomy with primary anastomosis. Thirty hours after surgery, he was found to have a fever of 102°F (38.8°C), blood pressure of 90/60 mm Hg, heart rate of 140 bpm, respirations of 24 breaths per minute, and low urine output. Physical examination showed diffuse abdominal tenderness. The surgical site is clean and Gram stain did not show any organism. Urinalysis (UA) was negative and the complete blood count (CBC) showed leukocytosis. Which of the following is the most likely cause of this patient's fever?

A. Pneumonia
B. Intraperitoneal leak from bowel injury
C. Surgical site infection
D. Deep tissue abscess

38.2 An 84-year-old nursing home resident underwent emergency open cholecystectomy under general anesthesia. She has advanced Parkinson's disease, hypertension, and diabetes, and who was receiving nutrition via nasogastric tube (NGT). On the second postoperative day, she was noted to be coughing and vomiting. Four days later, she had a temperature of 102°F (38.8°C), heart rate of 90 bpm, respiratory rate of 25 breaths per minute, blood pressure of 120/70 mm Hg, and oxygen saturation of 87% on room air. She had a productive cough with what the nursing staff describes as "putrid sputum." Lung auscultation showed crackles on the right and a chest radiograph revealed a patchy infiltrate in the right lung. Which of the following is the most appropriate next step in management?

A. Obtain an expectorated sputum sample for culture.
B. Treat empirically with antibiotics.
C. Insert a nasogastric tube.
D. Treat with an H_2-receptor antagonist.

38.3 A 42-year-old man underwent open reduction and internal fixation of a comminuted fracture of the right femur. He was doing well until the fifth postoperative day, when he complained of pleuritic chest pain and developed fever of 101°F (38.3°C), heart rate of 118 bpm, respiration of 30 breaths per minute, blood pressure of 130/85 mm Hg, and oxygen saturation of 85% on room air. His left ankle became edematous, warm, and tender. Which of the following is a risk factor for his condition?

A. Having an IV in his arm for more than 3 days
B. Failure to adequately use his incentive spirometer
C. Urinary bladder catheterization
D. Prolonged immobility

38.4 A 50-year-old woman with diabetes was recuperating from left inguinal hernia repair. Her glycosylated hemoglobin (HbA1c) prior to surgery was 10%. During postoperative follow-up a week after surgery, the surgical site was markedly erythematous, warm, and tender with pus. Which of the following is the next step in treatment?

A. Apply topical antibiotic to the surgical site.
B. Warm compresses alone will relieve the inflammation.
C. Open the surgical site and drain the infected material.
D. Send the patient home with prescription for oral antibiotics for 7 days.

ANSWERS

38.1 **B.** In the presence of severe hemodynamic changes and diffuse abdominal tenderness, intraperitoneal leak is the most common cause of fever in the first 36 hours after laparotomy.

38.2 **B.** This patient likely has aspiration pneumonia. She has risk factors including her age, functional status, recent general anesthesia, and advanced neurologic disease. She requires treatment with antibiotics which cover anaerobic bacteria. There is evidence that aspiration risk may be reduced by placing a nasogastric tube before surgery but long term use actually predisposes a person to aspiration pneumonia. Giving the patient a histamine H_2-receptor antagonist may also decrease the risk of aspiration by decreasing gastric acid secretion. It is a preventative measure. Expectorated sputum is unreliable for anaerobic cultures because of likely contamination by oral flora.

38.3 **D.** This patient has DVT and concomitant pulmonary embolism (PE). Risk factors include prolonged immobility, vascular damage, and hypercoagulability.

38.4 **C.** Incision and drainage is the most important therapy for SSI. Antibiotics are used solely in cases of significant systemic involvement.

Clinical Pearls

- Pulmonary complications, especially atelectasis, are the largest single cause of postoperative morbidity.
- Pneumonia is currently the leading cause of mortality from nonsurgical postoperative nosocomial infection. Mortality rate is 20% to 50%. Mechanical ventilation is the most important risk factor.
- UTI is the most common cause of nonsurgical postoperative nosocomial infection.
- The most common noninfectious cause of postoperative fever is drug fever.

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Case 39

You were busy seeing patients in your outpatient clinic when you heard a commotion coming from the waiting room. You went to check and found a very frantic mother and her 2-year-old son who is clutching his throat, coughing, drooling, and visibly struggling to breathe. The mother endorses that just a few minutes ago, the child was running around while eating grapes when she suddenly heard him gagging and wheezing. Her son has an appointment for well-child examination and he is apparently doing well. He has no significant history of respiratory illness. The toddler is still conscious but unable to talk, and his cough is becoming weaker. Breath sounds are decreased bilaterally, with wheezing and stridor heard on auscultation. You tried to ventilate the patient with the chin-lift maneuver but the chest fails to rise. You opened the mouth but you are unable to see any foreign object.

- What is the most likely diagnosis?
- What is the next step in the management of this patient?

ANSWERS TO CASE 39:

Acute Causes of Wheezing Other than Asthma in Children

Summary: A 2-year-old boy had acute onset of coughing, choking, drooling, and wheezing while eating grapes. He is unable to speak and his cough is weak. He was in a good state of health prior to the incident and has no history of respiratory illness. Physical examination reveals decreased breath sounds, wheezing, and stridor. There is no chest rise on ventilation attempt. No foreign object could be seen on his mouth.

- **Most likely diagnosis:** Foreign-body airway obstruction.
- **Next step in the management for this patient:** Heimlich maneuver (subdiaphragmatic abdominal thrusts).

ANALYSIS

Objectives

1. Identify the illnesses, other than asthma, that cause acute wheezing in children.
2. Understand the steps in the diagnosis and management of a wheezing child.

Considerations

Acute onset of wheezing in an otherwise healthy child similar to the above case should raise the suspicion for **foreign-body airway obstruction (FBAO).** Witnessed swallowing followed by choking is not necessary for diagnosis, but as much information should be gathered surrounding the onset of symptoms. FBAO is common among children age 6 months to 3 years old, accounting for approximately 70% of cases. Small toys and objects, balloons, and food (eg, nuts, grapes, and candies) are high-risk objects for aspiration. Older children may be able to identify the object they swallowed and assume the posture of clutching their neck with their hand **(universal choking sign).** Symptoms such as weak cough, inability to speak or cry, high-pitched sounds, or no sounds during inhalation, cyanosis, choking, vomiting, drooling, wheezing, blood-streaked saliva, and respiratory distress are clues to the diagnosis of FBAO. Physical findings of unilateral wheezing, unequal or decreased breath sounds, and stridor are common. In children, the foreign body could lodge on either side of the airway. If the foreign body lodges in the esophagus, acute wheezing is still possible when the obstruction compresses on the airways.

One should not attempt to remove the foreign object in a child who is actively coughing. Blind finger sweep is not recommended because of the danger of further obstruction or injury. Although the patient mentioned above is still conscious, he seems to have ineffective coughing and is beginning to get tired. Ventilation should be attempted while opening the airway with the head-tilt maneuver, which could also relieve the obstruction. In the above case, an attempt to remove the foreign object was initiated when ventilation was unsuccessful.

Since no foreign object is visualized, a series of **abdominal thrusts (Heimlich maneuver)** should be the next step to try to expel the foreign body. In infants, back blows and chest thrusts are performed instead of abdominal thrusts, which could cause iatrogenic trauma to the liver and stomach, which are not protected by the rib cage at that age. If the child continues to deteriorate even after 1 minute of resuscitative efforts and the above maneuvers fail to expel the foreign object, the emergency medical services (EMS) system should be activated while continuing cardiopulmonary resuscitation (CPR).

In the hospital setting, a bronchoscopic procedure is the treatment of choice. Chest x-ray is often normal, but in some cases shows a radiopaque foreign object or identifies localized hyperinflation and/or atelectasis. Most deaths from FBAO occur in children younger than 5 years of age; 65% are infants.

APPROACH TO Wheezing

DEFINITIONS

HEIMLICH MANEUVER: Performed by standing or sitting behind the person who is choking and placing the thumb side of one fist between the navel and the xiphoid process. The other hand grasps the fisted hand and a series of upward abdominal thrusts are delivered to create an "artificial cough" in a choking victim in an effort to dislodge the object blocking the airway.

STRIDOR: Wheezing coming from obstruction of the large airway that has a constant pitch and intensity throughout the entire inspiratory effort.

WHEEZING: A musical sound heard on pulmonary auscultation produced by the oscillating walls of airways that had been narrowed by mucus, inflammation, and so on.

CLINICAL APPROACH

Among the many causes of wheezing in children, asthma and viral infections are most common. Worldwide studies show that approximately 10% to 15% of infants wheeze in the first 12 months of life. The diagnosis of wheezing

hinges on accurate history, physical examination, laboratory tests, and even response to treatments. It is also important to gather information regarding the age of onset, exposure to cigarette smoke, presence of allergic signs and symptoms, frequency of wheezing, association with vomiting or feeding, and other accompanying symptoms.

The etiology of **acute wheezing** in children could be infectious (eg, bronchiolitis) or mechanical obstruction (eg, FBAO). **Recurrent wheezing,** on the other hand, encompasses anomalies of the tracheobronchial tree (eg, bronchomalacia), cardiovascular disease (eg, vascular rings and slings), gastroesophageal reflux, and immunologic disorders (eg, bronchopulmonary dysplasia, cystic fibrosis). This case concentrates on acute onset of wheezing other than asthma in children (Case 6 provides a more detailed discussion of asthma).

Bronchiolitis

Bronchiolitis is the most common acute cause of wheezing in children younger than 2 years of age, especially in infants who are 1 to 3 months old. Infants younger than 6 months are most severely affected, owing to smaller, more easily obstructed airways and a decreased ability to clear secretions. It is a viral infection causing nonspecific inflammation of the small airways and peaks during the winter months. **Respiratory syncytial virus (RSV) accounts for 70% of cases;** the rest are caused by parainfluenza, adenovirus, *Mycoplasma*, and metapneumovirus. These viruses elicit inflammatory and immune responses that produce mucus, edema, and cellular debris that block the small airways. The introduction of the influenza vaccine reduced the incidence of bronchiolitis caused by the flu virus.

Initially, the child develops rhinorrhea and wheezing followed by low-grade fever. On succeeding days, rhinorrhea will be more copious and the child may also experience cough, irritability, and varying degrees of dyspnea. As a result, the infant may have poor oral intake and possibly dehydration.

Profuse coryza, congestion, pharyngitis, nasal discharge, and fever usually characterize the clinical syndrome in children. Primary RSV infections are confined to the upper airways in more than 50% of patients. Symptoms reach a peak in 2 to 5 days, with involvement of the lower respiratory tract. Typical symptoms include cough, dyspnea, wheezing, and poor feeding.

Physical examination may reveal wheezing, fine crackles, prolonged expiratory phase, tachypnea, and increased work of breathing as evidenced by nasal flaring, intercostals retraction, and even apnea. Other physical findings often include otitis media, irritability, and hypothermia or hyperthermia.

The diagnosis of bronchiolitis is based on clinical presentation, the patient's age, seasonal occurrence, and findings from the physical examination. Tests are typically used to exclude other diagnoses, such as bacterial pneumonia, sepsis, or congestive heart failure, or to confirm a viral etiology and determine required infection control for patients admitted to the hospital.

Current literature does not support the routine use of laboratory tests as they do not alter clinical outcomes. If the diagnosis is doubtful or the clinical presentation is unusual, one may request a chest x-ray. Radiologic findings in individuals with bronchiolitis are variable and may include bronchial wall thickening, tiny nodules, linear opacities, atelectasis, patchy alveolar opacities, and lobar consolidation. A complete blood count (CBC) is usually normal. There are available assays for RSV and influenza that often are unnecessary, unless the patient is to be admitted and placed in a room with other RSV-positive infants. Sputum culture is requested if bacterial superinfection or pneumonia is suspected.

RSV bronchiolitis is a self-limited disease and can be safely managed in an outpatient setting. However, disease manifestation can be variable, and risk factors for severe disease include preexisting cardiac or pulmonary disease, premature birth, very young age (<2-3 months), nosocomial RSV infection, and, in some studies, low socioeconomic status. Patients who are in respiratory distress, younger than 3 months old or premature, those with comorbid conditions, lethargy, hypoxemia, or hypercarbia, and those with atelectasis or consolidation in chest radiograph need to be hospitalized.

The Agency for Healthcare Research and Quality (AHRQ), in collaboration with the American Academy of Family Physicians (AAFP) and the American Academy of Pediatrics (AAP), recommends **supplemental oxygen and supportive care as the modes of treatment with clear evidence of effectiveness in RSV bronchiolitis.**

Supportive care should consist of supplemental humidified oxygen, fluids, and the suctioning of nasal and pharyngeal secretions. The most important therapy is humidified oxygen. Medications have a limited role in the management of bronchiolitis. Several drugs are commonly used, but little or inconclusive evidence supports the routine use of any drug in the management of bronchiolitis. Nebulized bronchodilators, cool mist, steroids, antibiotics, ribavirin have insufficient evidence or have not been shown to help in previously healthy children. Steroids and bronchodilators may help if there is underlying asthma, but should be discontinued if initial trials fail to show significant clinical improvement.

Symptomatic treatment includes head elevation, suctioning of secretions after spraying the nasal passages with saline; antipyretics for fever; humidified oxygen for hypoxemia; and adequate hydration. If the infant is at high risk for aspiration, IV fluids may be the safest way to deliver nutrients. A therapeutic trial with albuterol, especially in infants with personal or family history of allergies, could identify a few responders. Parents of infants with bronchiolitis should be instructed not to expose the infant to cigarette smoke and educated on frequent handwashing to prevent transmission of the disease.

For infants with congenital heart disease or chronic lung disease, the antiviral agent ribavirin via aerosol can be considered, but has not been proven to alter mortality and length of illness. Administration of RSV immunoglobulin

(RespiGam) and palivizumab (Synagis) just before the beginning of RSV season are proven effective preventive therapy for children younger than 2 years who were born prematurely or who suffer from chronic lung disease. The cost-effectiveness of prophylaxis, however, is still debatable. In most cases, the illness is self-limited with usual duration of 2 to 4 days. A protracted course (months) can occur in around 20% of patients. Mortality is less than 1% and could be attributed to apnea, respiratory acidosis, and severe dehydration. The single best indicator of severity is low pulse oximetry. Indicators of mild disease include good po intake, age greater than 2 months, oxygen saturation greater than or equal to 94%, and age-based respiratory rate (< 45 0-2 months, < 43 2-6 months, and < 40 6-24 months). Children who had experienced bronchiolitis are at higher risk of developing asthma.

Croup

Croup is the most common cause of airway obstruction in children ages 6 months to 6 years old, and is the leading cause of hospitalization for children younger than 4 years old. It is **a viral infection that causes inflammation of the subglottic region** of the larynx that produces the characteristic barking cough, hoarseness, stridor, and different degrees of respiratory distress that are more severe at night. The croup syndrome encompasses **laryngotracheitis, laryngotracheobronchitis, laryngotracheobronchopneumonitis, and spasmodic croup.**

Croup usually occurs during fall and winter. Common organisms involved are parainfluenza, adenovirus, RSV, rhinovirus, Enterovirus, influenza viruses, and rarely, *Mycoplasma pneumoniae*. The prodrome is characterized by 12 to 72 hours of runny nose and low-grade fever. Hypoxia only occurs in severe cases. These symptoms peak from 1 to 2 days, and in most cases, resolve in 1 week.

Diagnosis is made through clinical presentation. However, imaging studies confirm the diagnoses. Frontal neck x-rays show the "steeple sign," which is indicative of subglottic narrowing of the tracheal lumen. When the diagnosis is uncertain, computed tomography (CT) scan of the neck offers a more sensitive evaluation.

Treatment is geared toward the severity of the croup (ie, the level of respiratory depression). Mild croup does not require any specific therapy, but a single dose of corticosteroid may reduce need for hospitalization. Moderate-to-severe croup entails a more comprehensive and intense approach.

Emergency management of croup should begin with assessment of airway obstruction; oxygen should be used liberally. There is no proof that humidified air is of value and mist tents should be avoided.

Hospitalize if severe croup is clinically apparent. Severe croup is exemplified by cyanosis, decreased level of consciousness, progressive stridor, severe stridor, severe retractions, markedly decreased air movement, toxic appearance, severe dehydration, and social factors limiting adequacy of outpatient monitoring. Children who are hospitalized with croup should be monitored closely and frequent physical examination needs to be performed.

The following medications should be avoided: sedatives, opiates, expectorants, bronchodilators, and antihistamines. Corticosteroids (nebulized, IM, or oral), and nebulized racemic epinephrine can be used in moderate to severe cases. Patients who receive epinephrine should be observed for 4 hours to monitor for rebound of symptoms.

Epiglottitis

Epiglottitis is a **bacterial infection of the supraglottic tissue** and surrounding areas that causes rapidly progressive airway obstruction. It usually affects children younger than 5 years old and is most commonly caused by bacteria such as *Haemophilus influenzae*, *H parainfluenzae*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *β-hemolytic streptococcus* A, B, and C. With the introduction of the *H influenzae* type b (Hib) vaccine, there has been a steady decline in cases of epiglottitis. Within 24 hours, the patient with epiglottitis would appear "toxic" and develop fever, severe sore throat, muffled speech ("hot potato voice"), drooling, and dysphagia. The child usually is noticeably anxious and assumes the sitting position, leaning forward on outstretched arms with chin thrust forward and neck hyperextended (tripod position) so as to increase the airway diameter.

With progression of airway obstruction, the patient may begin to have wheezing and stridor. **Epiglottitis is a medical emergency and visualization to confirm the presence of severely erythematous epiglottis is preferably done in the operating room** with experienced surgeon or anesthesiologist. The patient should be kept in a calm environment to prevent sudden airway obstruction. CBC usually shows leukocytosis, neutrophilia, and bandemia. The radiographic finding that is characteristic of epiglottitis is the **"thumb sign"** or protrusion of the enlarged epiglottis from the anterior wall of the hypopharynx seen on a lateral neck x-ray. Cultures of the blood and epiglottis yield the pathogenic bacteria. Treatment consists of appropriate antibiotics (oxacillin or nafcillin; cefazolin; clindamycin and ceftriaxone or cefotaxime) and airway management, usually in an ICU setting with a team ready to respond for intubation or tracheostomy. Death results from hypoxia, hypercapnia, and acidosis that lead to cardiorespiratory failure.

Abscesses

Deep abscesses of the neck are less common causes of acute wheezing, but they have the potential to be very serious. They are located in the peritonsillar, retropharyngeal, and pharyngomaxillary spaces.

Retropharyngeal abscess affects children 2 to 4 years. The abscess is usually caused by extension of pharyngeal infection, penetrating trauma, iatrogenic instrumentation, or foreign body. Children with this condition present with fever, drooling, dysphagia, odynophagia, stridor, and respiratory distress. Physical examination may indicate tender enlarged cervical lymphadenopathy, cervical spine ROM limitation, possible stridor, and wheezing. Diagnosis is

made by lateral neck films which show bulging in posterior pharynx (prevertebral soft tissue more abundant in children during expiration). Treatment utilizes antibiotics such as cephalosporins or antistaphylococcal penicillins. Incision and drainage is also an option.

Peritonsillar abscess is an infection of the superior pole of the tonsils and is more common in young teenagers. Fever, severe sore throat, muffled voice, drooling, trismus, and neck pain are typical symptoms. Enlarged tonsils with abscess, cervical adenopathy, and deviation of the uvula may be obvious on physical examination. CT scan of the neck is the most helpful diagnostic modality for identifying deep neck abscesses. The predominant pathogens are *Streptococcus pyogenes, S aureus,* and anaerobes. Ampicillin-sulbactam or clindamycin, if PCN allergic, for 14 days is appropriate treatment. Drainage of the abscess is indicated either as first-line treatment or when antimicrobial agents fail to produce adequate result. Serious complications from deep abscesses result from airway obstruction, septicemia, aspiration, jugular vein thrombosis/thrombophlebitis, carotid artery rupture, and mediastinitis.

Comprehension Questions

39.1 A 7-month-old baby was brought by her mother to an outpatient clinic because of a 2-day history of fever, copious nasal secretions, and wheezing. The mother volunteered that the baby has been healthy and has not had these symptoms in the past. The infant's temperature is noted to be 100.7°F (38.1°C), her respiratory rate is 50 breaths per minute, and her pulse oximetry is 95% on room air. Physical examination reveals no signs of dehydration, but wheezing is heard on bilateral lung fields on auscultation. The infant shows no improvement after three treatments with nebulized albuterol. Which of the following is the recommended treatment?

A. Continued nebulized albuterol every 4 hours
B. Antihistamines and decongestants
C. Antibiotics for 7 days
D. Initiate synagis
E. Supportive care with hydration and humidified oxygen

39.2 A 9-year-old girl is being seen in your office with fever and difficulty breathing. You are concerned about the diagnosis of epiglottitis. Which of the following is the most accurate statement regarding epiglottitis?

A. Child usually prefers to be in prone position.
B. Radiographic finding of "steeple sign."
C. Every effort should be made to visualize the epiglottis in the office to confirm the diagnosis.
D. Diagnosis is decreasing in incidence.

39.3 A 5-year-old child is brought into the office due to the mother's concern of difficulty breathing. On examination wheezing is noted. In which of the following conditions is antibiotic therapy most appropriate?

A. Asthma
B. Epiglottitis
C. Croup
D. Bronchiolitis
E. Foreign-body aspiration

39.4 A 12-year-old girl was brought to the emergency department because of severe sore throat, muffled voice, drooling, and fatigue. She had been sick for the past 3 days and is unable to eat because of painful swallowing. The parents deny any history of recurrent pharyngitis. The patient still managed to open her mouth and you were able to see an abscess at the upper pole of the right tonsil with deviation of the uvula toward the midline. Examination of the neck reveals enlarged and tender lymph nodes. Which of the following is the most appropriate management?

A. Analgesics for pain
B. Oral antibiotics
C. Nebulized racemic epinephrine
D. Incision and drainage of the abscess
E. Tonsillectomy and adenoidectomy

ANSWERS

39.1 **E.** Bronchiolitis is the most likely diagnosis in this case. There is no established treatment for bronchiolitis except for supportive management of the patient's symptoms. Because the infant did not respond to an albuterol trial, there is no justification for continuing its use. Antihistamines, decongestants, and antibiotics are not effective. Synagis is not helpful in the acute setting.

39.2 **D.** The incidence of epiglottitis has markedly reduced since the introduction of the Hib vaccine. Children with epiglottitis are more likely to be in the tripod position than prone. The "steeple sign" is seen in croup; the "thumb" sign is seen in epiglottitis. Visualization of the epiglottis should preferentially occur in an operating room, where immediate intubation or tracheostomy can occur.

39.3 **B.** Epiglottitis is usually a bacterial infection treated with antibiotics.

39.4 **D.** This patient is suffering from peritonsillar abscess. Of the choices listed, incision and drainage is the most appropriate. Tonsillectomy is only indicated if there are confirmed cases of **recurrent** pharyngitis and peritonsillar abscess.

Clinical Pearls

- Sufficient airflow is required for the airway to produce a wheezing sound. Disappearance of wheezing in a patient who initially presents with wheezing is an ominous sign that suggests complete blockage of the airway or imminent respiratory failure.
- Bronchiolitis is the most common lower respiratory disease of infants and the most common reason for hospitalization for infants younger than 1 year old.
- Never perform a blind finger sweep of a foreign object aspirated by an infant or child.
- Epiglottitis is a medical emergency.

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Case 40

A 28-year-old white woman presents to your office with a chief complaint of constipation and abdominal pain. On further questioning, she reports she has had this problem since beginning college at the age of 18 years. Her symptoms have waxed and waned since this time, but never have worsened. She describes her abdominal pain as dull, crampy, and nonfocal but more prominent in the left lower quadrant, and sometimes relieved with defecation. She denies radiation of pain, nausea, vomiting, fever, chills, weight loss, heartburn, or bloody or dark stool. She reports having a bowel movement every 1 to 2 days that is hard and feels incomplete. She has tried over-the-counter remedies, including stool softeners and antacids, but only experienced minimal improvement in her symptoms. She only takes birth control pills and denies any use of herbs or laxatives. Her family history is negative, including for colorectal cancer and inflammatory bowel disease, and she reports that her parents and siblings are healthy. She is currently engaged and reports significant stress in preparing for the wedding. On physical examination, you note her to be somewhat anxious, but otherwise in no apparent distress. Her vital signs and a general physical examinations are normal. Her abdomen has normal bowel sounds, no tenderness on superficial and deep palpation, and no rebound, rigidity, or guarding. Liver and spleen size are within normal limits and no masses are palpable. Pelvic examination is normal. Rectal examination shows normal sphincter tone, no masses, and brown stool that is occult blood negative.

- What is your most likely diagnosis?
- What is your next diagnostic step?
- What is the next step in therapy?

ANSWERS TO CASE 40:
Irritable Bowel Syndrome

Summary: A 28-year-old woman presents with a several-year history of abdominal pain and constipation. She denies any fever, weight loss, heartburn, or bloody stools. Her past medical history and family history are otherwise unremarkable. The physical examination, including abdominal and pelvic examination, are grossly within normal limits.

- **Most likely diagnosis:** Irritable bowel syndrome.
- **Most appropriate next step:** In the absence of any GI alarm features, a complete blood count and stool Hemoccult test for initial screening.
- **What is the next step in therapy?** Trial of fiber supplementation.

ANALYSIS

Objectives

1. Describe the epidemiology, clinical manifestations, and pathophysiology of irritable bowel syndrome.
2. Learn the diagnostic approach to irritable bowel syndrome and rationale for ordering diagnostic studies based on symptom subtype and/or presence of "alarm features."
3. Review current therapeutic strategies in the patient with irritable bowel syndrome.
4. Recognize the role of psychosocial factors in irritable bowel syndrome.

Considerations

This is a young woman with long-standing abdominal pain and constipation. She denies any "alarm features" like weight loss, bloody stools, fever, and refractory diarrhea, and her family history is negative for colon cancer or inflammatory bowel disease. The chronicity and lack of worsening of her symptoms coupled with her young age points to a functional GI disorder, such as irritable bowel syndrome. The presence of fever, weight loss, or an abnormal physical examination would be other worrisome findings. A reasonable workup in this case should include stool for guaiac and a complete blood count.

APPROACH TO
Suspected Irritable Bowel Syndrome

DEFINITIONS

IRRITABLE BOWEL SYNDROME (IBS): This is a functional GI disorder characterized by chronic abdominal pain and altered bowel habits.

LUBIPROSTONE (AMITIZA): Pharmacologic agent that selectively activates intestinal chloride channels and increases fluid secretion is FDA approved for IBS in women with constipation, but has a side effect of nausea in significant percentage of patients.

CLINICAL APPROACH

The prevalence of IBS is approximately 10% to 15% of the US population and accounts for a large proportion of GI complaints seen both by primary care physicians and gastroenterologists. **IBS affects women two to three more times often than men** and patients typically present in the second or third decades of life, although virtually any age group can be affected. Despite studies to elucidate the underlying physiologic abnormalities seen in IBS, the pathophysiology of IBS remains unclear. Several studies show abnormal gut hypersensitivity to visceral perception and pain, altered gastrointestinal motility, and dysregulation of the brain–gut axis through increased reactivity to stress. A high prevalence of psychopathology is seen in patients who are eventually diagnosed with IBS. Although the association between psychological disturbances and IBS are complicated and not clearly defined, psychiatric symptoms appear to predict illness behavior rather than directly cause IBS. IBS also commonly coexists with other functional disorders such as fibromyalgia, lower back pain, and chronic headaches.

Patients with IBS complain of constipation, diarrhea, alternating constipation with diarrhea, and periods of normal bowel habits that alternate with either constipation and/or diarrhea. The abdominal pain associated with IBS is frequently in the lower part of the abdomen, with the left lower quadrant being the most common location. However, both the location and the nature of the pain in IBS are subject to great variability. The pain is described as a cramping sensation of intermittent frequency and variable intensity, often improved or relieved with defecation. Abdominal pain usually does not wake a person up from sleep in IBS. However, severe cases of IBS may be accompanied by nighttime awakenings. Other gastrointestinal symptoms seen in IBS include the passage of mucus with stool, bowel urgency, bloating, and the sensation of incomplete stool evacuation. Up to 50% of people with IBS also suffer from upper GI symptoms such as dyspepsia, nausea, and gastroesophageal reflux.

Table 40–1 ROME III DIAGNOSTIC CRITERIA FOR IRRITABLE BOWEL SYNDROME

Recurrent abdominal pain or discomfort at least 3 d/mo for the past 3 months, associated with two or more of the following:
- Improvement with defecation
- Onset associated with a change in the frequency of stool
- Onset associated with a change in form (appearance) of stool

Criteria must have been fulfilled for the past 3 months, with symptoms onset at least 6 months before diagnosis. On the basis of the predominant bowel habit, IBS has been categorized into one of the following subgroups:
- IBS with diarrhea (more common in men)
- IBS with constipation (more common in women)
- IBS with mixed bowel habits

Each group accounts for about one-third of all patients.

Reproduced from Mayer EA. Clinical practice. Irritable bowel syndrome. *N Engl J Med.* 2008 Apr 17;358(16):1692-1699.

Diagnosis

In an effort to objectively diagnose a patient with IBS, the Rome Criteria (Table 40–1) were developed and subsequently revised. Based on the presence of positive symptoms and the absence of structural or biochemical explanation of the symptoms, a patient may be diagnosed with IBS. Physicians are encouraged to avoid unnecessary and expensive studies and instead to use judicious cost-effective diagnostic testing.

A thorough history should be obtained using open-ended, nonjudgmental questions. The physical examination should focus on ruling out organic pathologic processes that are inconsistent with IBS. Importance should be paid to all medications and dietary habits that may worsen or mimic the symptoms of IBS.

The differential diagnosis of IBS can be very broad. Patients should be asked for the presence of "alarm features," (Table 40–2) which include fever, anemia, involuntary weight loss greater than 10 lb, hematochezia, melena, refractory or bloody diarrhea, and a family history of colon cancer or inflammatory bowel disease. The **presence of alarm features usually points to an underlying organic etiology**, such as inflammatory bowel disease or colon cancer, and may warrant further workup, including laboratory, endoscopic, and/or radiographic testing.

In the patient with typical features of IBS and the absence of alarm features, a complete blood count and stool Hemoccult are appropriate initial screening tests. Because of the high pretest probability of neoplasm in patients age 50 years or older, a colonoscopy is recommended in addition to any other

Table 40–2 ALARM FEATURES WARRANTING FURTHER WORKUP

Weight loss
Fever
Melena
Blood in stool
Excessive diarrhea
Older age
Anemia
Family history of colon cancer
Family history of inflammatory bowel disease
Sudden onset of symptoms
Major change in symptoms

diagnostic workup in this age group. A sigmoidoscopy or colonoscopy can be performed on the younger patient if inflammatory bowel disease is suspected, or if the patient has additional alarm features, such as refractory diarrhea or unintentional weight loss.

Treatment

Based on the predominant symptom subtype, empiric therapy can be initiated to control a patient's symptoms. For abdominal pain, the use of antispasmodics, such as dicyclomine and hyoscyamine, may be used on an as-needed basis, especially when pain is mild and infrequent. Low-dose tricyclic antidepressants (TCAs) should be considered when pain is more frequent and severe. Selective serotonin reuptake inhibitors (SSRIs) may be beneficial when depression or anxiety disorders are comorbid with IBS.

For constipation-predominant IBS, increasing fiber intake, either via dietary fiber, synthetic fiber, or natural fiber, is recommended. For diarrhea-predominant IBS, loperamide may reduce the frequency of loose stools, as well as decrease bowel urgency.

Tegasorad (Zelnorm) and Alosetron (Lotronex), which act at the serotonin (5-HT) receptor, have been shown to help with the pain associated with IBS. However, due to an increased incidence of ischemic cardiovascular events and ischemic colitis, tegaserod has been withdrawn from the US market and alosetron has restricted access. Lubiprostone (Amitiza), which selectively activates intestinal chloride channels and increases fluid secretion is FDA approved for IBS in women with constipation, but has a side effect of nausea in significant percentage of patients.

Pharmacologic agents should be used as adjuncts in the overall treatment plan. A multifactorial approach, including modification of diet and lifestyle, providing patient education and reassurance, and medication therapy is often

required. For patients with significant psychosocial issues, psychotherapy, stress management, and treatment of underlying psychiatric disorders appear to be helpful in overall symptom management. Cognitive behavioral therapy has shown to be especially helpful. As always, a therapeutic physician–patient relationship is critical to maximizing the best clinical outcome. It is important that the physician not appear dismissive of the patient's complaints and communicate to the patient that the symptoms are real and not just in his or her head.

Comprehension Questions

40.1 A 65-year-old man reports a lifelong history of IBS with alternating bouts of constipation and diarrhea. He denies any so-called alarm symptoms, but does report that his symptoms have worsened over the last several months. He reports never having a colonoscopy before. Stool is negative for blood and leukocytes. Which of the following is the most important next step?

A. Esophagogastroduodenoscopy (EGD)
B. Begin trial of the 5-HT agonist tegaserod
C. Explore possible underlying psychiatric symptoms
D. Colonoscopy
E. Increase fiber intake

40.2 A 37-year-old woman reports a 10-year history of intermittent abdominal pain, and constipation alternating with diarrhea. She has no weight loss, fever, or worrisome features on examination. Which of the following agents is clinically indicated as a first-line treatment for mild to moderate abdominal pain associated with IBS?

A. Amitriptyline
B. Lubiprostone
C. Dicyclomine
D. Fluoxetine

40.3 A 27-year-old graduate student in psychology is been evaluated for intermittent abdominal pain. She is diagnosed with irritable bowel syndrome. She asks whether there is a relationship between psychiatric disorders and IBS. Which of the following statements is most accurate?

A. IBS is usually caused by the underlying psychiatric disorder.
B. Psychiatric conditions may worsen coexisting IBS.
C. Successfully treating the psychiatric comorbidity causes remission of IBS.
D. No evidence supports a relationship between IBS and psychiatric disorders.

40.4 A 26-year-old college student has been increasingly stressed before final examinations. She has been using over-the-counter antacids more days out of the week than not for an upset stomach and feeling full immediately after eating. She typically has one bowel movement per week and there is no blood in the stool. She feels immediate relief after passage of stool and flatulence. For the patient with constipation-predominant IBS, which of the following is the best first-line therapy?

A. Hyoscyamine
B. Sertraline
C. Psyllium
D. Loperamide

40.5 A 25-year-old woman comes to your office worried that she might have IBS, which she heard about on the news. She reports abdominal pain and diarrhea for 3 months. She also reports observing blood in her stool several times. She is worried what impact her constantly having to use the bathroom is having on her job as a lawyer. Her physical examination is normal except for a hemoccult-positive test after a rectal examination. While looking over her records you notice that she has lost 20 lb since she last saw you 3 months ago. Which of the following is an appropriate next step?

A. Refer her for cognitive behavioral therapy.
B. Offer her symptomatic relief with loperamide.
C. Recommend that she take fiber for better bowel regulation.
D. Obtain colonoscopy.

ANSWERS

40.1 **D.** Age-appropriate cancer screening (colonoscopy) is indicated, even in the setting of an established diagnosis of IBS, because of the high pretest probability of detecting an underlying neoplasm.

40.2 **C.** Dicyclomine, an antispasmodic anticholinergic medication, can be used on an as-needed basis for mild-to-moderate abdominal pain associated with IBS. For more persistent and severe pain, low-dose TCAs, like amitriptyline, are beneficial. Lubiprostone is indicated in women with constipation-predominant IBS as a second-line agent.

40.3 **B.** Comorbid psychiatric disorders typically worsen IBS symptomatology, but have not been shown to cause IBS directly. Successfully treating an underlying psychiatric disorder may improve symptoms of IBS, but will not likely resolve all symptoms of IBS.

40.4 **C.** Fiber supplementation is considered first-line therapy in constipation-predominant IBS. It is effective and safe, and available without prescription.

40.5 **D.** This patient presents with alarm signs of blood in the stool and weight loss. Although psychiatric problems or irritable bowel syndrome are possible, more serious conditions should be evaluated and ruled out. A CBC, erythrocyte sedimentation rate, and colonoscopy or radiological study assessing for inflammatory bowel disease would be prudent.

Clinical Pearls

- The pathophysiology of IBS is not clearly elucidated. However, altered gut motility, visceral hypersensitivity, and dysregulation of the brain gut axis, coupled with psychosocial factors, appear to influence IBS symptoms in varying degrees.
- The symptom complex of altered bowel habits and chronic abdominal pain is the hallmark of IBS. Symptoms typically begin early in life, wax and wane, and occur in the absence of any organic cause.
- Alarm features may indicate an underlying organic pathology and require additional diagnostic workup that may include laboratory, radiologic, and/or endoscopic studies.
- Treatment should be symptom-specific and should include appropriate use of medication, dietary and lifestyle changes, and examination of any psychosocial factors that contribute to IBS symptoms.

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Case 41

A 30-year-old woman presents to the clinic complaining of feeling depressed and jittery. She has been feeling this way on and off for the last year, since her husband divorced her. She has 3 children, ages 12, 5, and 2 years. She reports an increase during the past 3 months of headaches, difficulty sleeping, loss of appetite, crying spells, and increased irritability. When asked about substance use, she says she drinks wine at night to help her sleep. Further questioning leads her to disclose that she started drinking more after her husband left, and she currently drinks, on average, 1.5 bottles of wine every evening, and sometimes more on the weekends. She does not use illicit drugs. She has no prior history of psychiatric disorders. The patient's physical examination is unremarkable with the exception of an elevated blood pressure (140/90 mm Hg). Routine laboratory tests from her last visit 1 month ago indicate an elevated γ-glutamyltransferase (GGT) of 220 IU/L.

- What is the most likely diagnosis?
- What is your next step?

ANSWERS TO CASE 41:

Alcohol Dependence/Substance-Induced Depressive Disorder

Summary: A 30-year-old, physically healthy woman presents to an outpatient clinic with depressive symptoms that became clinically significant after increased use of alcohol to cope with stress. There is no previous history of psychiatric disorder or physical illness that could account for the symptoms.

- **Most likely diagnosis:** Alcohol dependence with a secondary substance-induced depressive disorder.
- **Next steps:** Assess severity of alcohol problem using standardized screening questions; assess for suicidality; assess social support network; deliver a brief intervention consisting of recommendation for reducing or quitting drinking; and referral for substance abuse and/or mental health treatment.

ANALYSIS

Objectives

1. Know brief alcohol screening questions (and cut point) for use in clinical practice.
2. Know the diagnostic criteria for alcohol abuse and dependence.
3. Know the definition of "at-risk" drinking.
4. Know what constitutes a standard drink.
5. Understand the distinction between substance-induced and non–substance-induced depression.
6. Know the signs and dangers of alcohol withdrawal.
7. Know components of a brief, office-based intervention for alcohol abuse and dependence.

Considerations

This is a 30-year-old woman who has admitted to drinking more alcohol since being divorced from her husband. She has some of the findings of alcohol abuse such as hypertension, elevated liver enzymes, and depression. She also reports some jitteriness which likely indicates tremors with alcohol withdrawal. Other drug or medication use should be assessed. Psychiatric disorders, such as depression or bipolar disorder, should also be in the differential diagnosis. Once alcohol dependence is suspected, then a detoxification process is critical to the patient being successfully treated.

APPROACH TO
Suspected Alcohol Dependence

DEFINITION

ALCOHOL ABUSE: Harmful use of alcohol which can be either physical or mental harm. Alcohol abusers drink despite recurrent social, interpersonal, and legal problems as a result of alcohol use.

ALCOHOL DEPENDENCE: Mental and physical need to consume alcohol in order to prevent the pains of withdrawal and obtain certain results, and associated with increasing consumption to obtain same effect (tolerance).

CLINICAL APPROACH

Epidemiologic studies have shown that alcohol use disorders are among the most prevalent of medical, behavioral, or psychiatric disorders in the general population. There is a documented prevalence of alcohol abuse and dependence estimated to be between 7% and 10% in the United States. Despite higher thresholds and tolerance, in general, men are at least twice as likely to meet criteria for alcohol abuse and dependence.

In patients reporting depressive symptoms, it is important to assess for current substance abuse, particularly alcohol, cocaine, and methamphetamine. If used in excess, these substances and their associated withdrawal syndromes can result in depression. Whether determined to be substance-induced or not, the depressive symptoms should be taken seriously. An assessment for suicidality (current and past) and current sources of family/social support should be conducted. The potential for significant alcohol withdrawal should also be assessed. If depressive symptoms persist longer than 4 weeks after discontinuation of alcohol, consider other potential causes of depression.

ASSESSMENT

Alcohol Screening

Brief screening instruments have been developed in order to identify potential alcohol abuse or dependence.

The **most commonly used instrument is the CAGE.** The CAGE was designed for rapid verbal screening for alcohol abuse and dependence in clinical practice. CAGE **is a mnemonic representing the following four items**:

- Have you ever felt you should **c**ut down on your drinking?
- Have people **a**nnoyed you about your drinking?

- Have you ever felt bad or guilty about your drinking?
- Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover (eye-opener)?

A positive response to two or more of the above questions is considered a positive screen. Systematic reviews of this screening test show a sensitivity of 65% to 69% and specificity of 92% to 93%. The effectiveness of the CAGE instrument varies with gender, ethnicity, age, and other differences. It is less effective in detecting binge drinking.

The AUDIT-C (Alcohol Use Disorders Identification Test) was better at detecting at-risk, hazardous, or harmful drinking. A score of 3 or greater was considered a positive screen.

- "How often do you have a drink containing alcohol?"—0 points for never, 1 point for monthly or less, 2 points for 2 to 4 times/month, 3 points for 2 to 3 times/week, 4 points for 4 days/week or more.
- "How many drinks containing alcohol do you have on a typical day when you are drinking?"—0 points for not drinking, 1 point for 1 to 4 drinks, 2 points for 5 to 6 drinks, 3 points for 7 to 9 drinks, 4 points for 10 or more drinks.
- "How often do you have 6 or more drinks on one occasion?"—0 points for never, 1 point for less than monthly, 2 points for monthly, 3 points for weekly, 4 points for daily or almost daily.

Alcohol Dependence versus Abuse

A diagnosis of *alcohol dependence* is defined by *DSM-IV* TR (*Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, text revision) when the patient exhibits a maladaptive pattern of alcohol use leading to significant impairment or distress and three or more of the following within 12 months

- Need for markedly increased amounts of alcohol to achieve intoxication or desired effect, or markedly diminished effect with continued use of the same amount of alcohol
- Alcohol withdrawal syndrome, or use of substances to relieve or avoid withdrawal symptoms
- Persistent desire or unsuccessful efforts to cut down or control drinking
- Drinking more than intended
- Giving up or reducing activities due to drinking
- Considerable time spent in activities to obtain alcohol, drink, or recover from alcohol effects
- Continued drinking despite knowledge of having persistent or recurrent physical or psychological problems exacerbated by alcohol use
- Considered physical dependence (in addition to psychological dependence) if evidence of tolerance or withdrawal

A diagnosis of *alcohol abuse* is defined by *DSM-IV* TR when the patient exhibits a maladaptive pattern of alcohol use leading to significant impairment or distress, does not meet the criteria for alcohol dependence, but does exhibit one or more of the following within 12 months:

- Recurrent drinking resulting in failure to fulfill major role obligations
- Recurrent drinking in situations in which it is physically hazardous
- Recurrent alcohol-related legal problems
- Continued alcohol use despite persistent or recurrent social or interpersonal problems caused or exacerbation by alcohol

At-Risk Drinking

Patients may not meet *DSM-IV* criteria for alcohol abuse or dependence, but may still be considered "at-risk" for problems related to alcohol, particularly health-related problems. The National Institute on Alcoholism and Alcohol Abuse (NIAAA) defines moderate drinking as follows:

- Men: less than or equal to two drinks per day
- Women: less than or equal to 1 drink per day
- Over 65 years: less than one drink per day

The NIAAA defines at-risk drinking as:

- Men: more than 14 drinks per week or more than 4 drinks per occasion
- Women: more than seven drinks per week or more than three drinks per occasion

Binge drinking, which is more common in young adults, is defined by NIAAA as: "A pattern of drinking that brings blood alcohol content to 0.08% in the past month. This typically represents more than or equal to 5 drinks for a male or more than or equal to 4 drinks for a female in approximately 2 hours."

Standard Drink Measurement

A standard drink represents 14 g of pure alcohol, typically one (12 oz) beer, one (5 oz) glass of wine, or one shot (1.5 oz) of spirits (eg, whiskey, gin, vodka). When assessing for at-risk drinking, it is important to clarify the number of standard drinks a patient is consuming in a day or week. For example, a patient may report he drinks only two beers each day, but the beers to which he is referring may be large, 48-oz cans, equaling four standard drinks each.

Substance-Induced Depression versus Primary Depression

A substance-induced mood disorder is distinguished from a primary mood disorder typically by considering the onset and course of the two disorders. **Depression only arising in association with alcohol intoxication or withdrawal**

states is likely to be substance induced. If depressive episodes are reported prior to substance use or occur during times of sustained abstinence or are substantially in excess of what would be expected given the type or amount of the substance used or the duration of use, then the mood disorder is likely to be primary. Withdrawal states can be relatively protracted and substance-induced mood symptoms may be evident up to 4 weeks after the cessation of substance use. The importance of this distinction lies in the chosen treatment plan. **Antidepressant medication is likely to be ineffective, if not harmful, to a patient with a significant alcohol (or other substance) problem.** Referral to substance abuse treatment should be the first choice of treatment in such cases, with follow-up for reassessment of depressive symptoms, about 1 month postabstinence.

Alcohol Withdrawal

Alcohol withdrawal may not be immediately obvious if a patient has ingested alcohol in the past 12 hours. Signs and symptoms to notice or assess for include tremulousness ("shake" or "jitters," which can occur within 6 hours of abstinence), insomnia, anxiety, depressed mood, gastrointestinal upset, heart palpitations, and sweating. More severe symptoms associated with a long history of chronic alcoholism include generalized tonic-clonic seizures (within 6-48 hours), hallucinations (within 12-48 hours; typically visual but can be auditory or tactile), and delirium tremens (DTs; within 48-72 hours), which is characterized by hallucinations, agitation, tremor, sleeplessness, and sympathetic hyperactivity. DTs only occur in approximately 5% of patients with withdrawal symptoms, but this is a serious condition with in-hospital mortality of 5% to 10%, usually from arrhythmias or infections. Benzodiazepines or phenobarbital are the drugs of choice for managing alcohol withdrawal.

INTERVENTION

Brief, Office-Based Intervention for Alcohol Abuse and Dependence

Research indicates that a brief **5 to 10 minute discussion between physician and patient can lead to significant reductions in risky and hazardous drinking.** The Brief Negotiation Interview is a brief intervention for substance abuse that can be conducted in fewer than 10 minutes and is ideally suited for use in busy clinical settings. The main point to keep in mind is that this approach is nonconfrontational, nonjudgmental, and proceeds based on how ready the client is to make any changes with regard to alcohol use. Rather than lecturing and reprimanding, a physician can initiate a discussion about the patient's drinking and provide feedback so as to increase a patient's *own*

internal motivation and help resolve ambivalence about changing. There are five components to this intervention:

1. Establish rapport.
2. Ask permission to discuss alcohol use.
3. Provide feedback.
4. Assess readiness.
5. Enhance motivation, negotiate, and advise.

Establishing rapport and asking permission to discuss alcohol use ("I have some concerns about your alcohol use and I'm wondering if we can discuss this today.") will reduce patient resistance. Information or feedback about the patient's current drinking level, associated risks to one's health, and recommended drinking levels should be provided. Many patients are unaware of the healthy drinking limits established by the NIAAA. In the current case, it would also be important to express empathy with the stressors the patient is facing, and to note that some people use alcohol to cope, and this can lead to alcohol-induced depression.

The next step is to ask patients to rate how ready they are to reduce their drinking to below-risk levels, or to quit drinking entirely (which is recommended for people diagnosed with alcohol dependence). Ask patients to rate how ready they are to reduce or quit using alcohol on a scale from 1 to 10, where 1 is "not at all ready" and 10 is "completely ready and wants help making a plan."

For patients who are not currently motivated to change their alcohol use, make sure their viewpoint is acknowledged, using statements such as, "it sounds like you are not quite ready to change right now." Questions like, "what might have to happen for you to decide to work on changing," are also appropriate and will prompt further thinking about the issue. Another effective strategy is to ask clients who rate their readiness in the low range, "Why did you rate yourself a 3 (or 4 or 2) and not a 1?" This question usually elicits "change talk," or causes the patient to talk about why change would be beneficial. After a brief discussion, offer a phone number or brochure for available treatment options, and explain that if they do decide to seek help, services are available.

For patients who are ready to make changes, ask whether they can make a commitment to a goal, what that goal is, and what they can use to help them achieve this goal. Things to consider include social support (eg, church) or treatment options including free community support groups (eg, 12-step meetings), psychotherapy, and medication management. Writing down the plan to which they agree and asking them to sign it is a final tool that can help solidify their commitment to making the change. It is important to assess the risk of withdrawal symptoms based on quantity and chronicity of alcohol use and make appropriate arrangements for supervised, medically assisted detoxification, when appropriate.

In summary, it is important to clearly convey, in a nonjudgmental manner, the levels at which drinking is risky, concern about the impact of a patient's

alcohol use, and to provide a recommendation to reduce drinking. For patients with a substance-induced mood or anxiety disorder, physicians should suggest that stopping or reducing alcohol use may reduce or eliminate problematic psychological symptoms (eg, depression). Offering referrals for psychotherapy, 12-step meetings, or alcohol detoxification/treatment programs is a final and critical component of care.

Comprehension Questions

41.1 A 65-year-old male smoker, presents to the office for epigastric pain off and on for the last 4 months which is partially alleviated by over-the-counter antacids and ranitidine. His examination shows mild epigastric tenderness and liver edge 2 cm below costal margin. Laboratory values show elevated GGT, AST/ALT elevation with ratio greater than 2, elevated prothrombin time, macrocytosis, thrombocytopenia, and hypoalbuminemia. His stool is trace heme positive on rectal examination. His brother died of colon cancer at age 66. His last colonoscopy was at age 50. Which of the following is the most likely underlying diagnosis?

A. Viral hepatitis
B. Alcoholic liver disease
C. Chronic pancreatitis
D. Gastroesophageal reflux disease
E. Colonic adenocarcinoma

41.2 A 55-year-old CEO of a financial investment firm has been losing clients at an increasing rate over the last 6 months. For most of his life he would have a 4 oz glass of scotch after work. Beginning almost a year ago he started consuming at least three of these after work, sometimes even finishing a bottle. In the last 6 months he has had to have a drink in the morning to prevent shakes while at work. More and more frequently he has been showing up late to work or missing meetings. Which of the following is an example of secondary prevention of alcoholism?

A. Raising the minimum drinking age
B. Breath alcohol testing for regulated truck drivers
C. Referral of diagnosed alcoholic to Alcoholics Anonymous
D. Limiting alcohol sales on Sunday

41.3 A 65-year-old man states that he drinks about 16 oz of beer each evening with a friend after work. His wife is telling him he drinks too much. She does not drink at all. He does not think this is much because he used to consume at least a six-pack each day on the weekend watching football when he was in his thirties. He has never had a DWI (driving while intoxicated) or an amnesic episode after drinking. Approximately how many standard drinks does this amount of beer equal and which of the following category of drinker would you classify him as?

A. 1.3; moderate drinker
B. 1.3; at-risk drinker
C. 1.5; social drinker
D. 1.5; alcohol dependent

41.4 A 45-year-old man presents for his annual physical examination. On his last physical he was found to have total cholesterol of 250 mg/dL, low-density lipoprotein (LDL) of 165, and high-density lipoprotein (HDL) of 32. After a trial of diet and exercise that did not improve his lipid levels, he was placed on simvastatin. Today he reports no changes in bowel or bladder habits and no myalgias. He is found to have elevated blood pressure and a slight hand tremor. His father developed Parkinson disease at age 67. He admits that he drinks heavily, but has no interest in changing his behavior. He feels badly at times, but states that in the past he has tried to reduce his alcohol consumption without effect. Which of the following is the most appropriate next step in management?

A. Administer the CAGE questionnaire.
B. Refer the patient to Alcoholics Anonymous.
C. Postpone discussion of alcohol cessation until patient expresses willingness to modify his behavior.
D. Recommend that the patient decrease his drinking after assessing his readiness to change.
E. Tell the patient about the risks of heavy drinking, including alcohol related peripheral neuropathies.

ANSWERS

41.1 **B.** Alcoholic liver disease. The pattern of liver enzymes is consistent with the whole body effects of chronic heavy alcohol ingestion. ALT is elevated greater than AST in conditions that are more specific to the liver. Hematologic change is indicative of marrow toxicity that is seen in alcohol abuse. The elevated prothrombin time and low albumin indicate significant impairment of liver protein production.

41.2 **B.** Breath alcohol testing of regulated truck drivers is an example of secondary prevention of alcoholism. Raising the drinking age and limiting sales are examples of primary prevention. Referral of a diagnosed alcoholic to Alcoholics Anonymous is a tertiary prevention.

41.3 **B.** One 16 oz beer equals 1.3 standard drinks (one 12 oz beer = 1 standard drink). NIAAA defines moderate drinking in males over 65 and women as less than or equal to one drink per day.

41.4 **D.** With patients who are not motivated to change, arguing or insisting they change is unlikely to be effective. Their opinions and choices should be acknowledged, followed by a brief discussion of the patient's drinking and potential consequences, a recommendation to cut down or stop, and a referral.

Clinical Pearls

- Alcohol and other drug abuse can significantly impact both physical and mental health.
- Assess whether the onset of depression or other mental health/behavioral problems preceded or followed significant alcohol or other drug abuse or dependence, to determine the primary problem and associated treatment.
- Alcohol dependence is characterized by tolerance, withdrawal, drinking larger amounts or for longer periods over time, desire or unsuccessful efforts to control use, much time spent drinking, reduction in other life activities, and continued use despite drinking-related physical and psychological problems.
- Alcohol withdrawal symptoms can be life threatening. Supervised, medically assisted detoxification may be necessary for long-term, chronic alcoholism.
- Brief, physician-delivered alcohol interventions are effective for reducing problematic drinking.
- "Finger wagging," scolding, or lecturing patients tends to engender resistance to change; a physician's advice can have a much more powerful effect if delivered in a nonjudgmental, nonconfrontational manner.

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Case 42

A 35-year-old woman presents to your office complaining of skipped or "irregular beats" for the past few weeks. She paid little attention to her symptoms because she had been under job-related stress and she thought these symptoms would disappear. Instead, her occasional skipped beats increased in frequency to twice a day, lasting up to 2 minutes. Her father, who suffered from heart disease, urged her to see a doctor. There had been no chest pain, shortness of breath, or dizziness. She consumes about two cups of coffee a day. She recently tried some diet pills to lose weight but stopped this medicine when her symptoms became more frequent. On examination, she is of average build. Her blood pressure is 130/85 mm Hg, her heart rate is 92 bpm, and her temperature is 98.6°F (37°C). Head, ears, eyes, nose, and throat (HEENT) examination is normal. No conjunctival pallor noted. Neck examination is supple. No jugular venous distension. Thyroid gland is normal size without nodules and is nontender. There are no associated thyroid bruits. Lung examination is normal. Cardiac examination reveals regular rate and rhythm with normal S_1 and S_2. No midsystolic click is heard. Abdominal and extremity examinations are normal. Neurologic examination reveals no resting tremor. Reflexes are normal.

- What is your most likely diagnosis?
- What is your next diagnostic step?
- What is the next step in therapy?

ANSWERS TO CASE 42:
Palpitations

Summary: A 35-year-old woman presents to your office with a few weeks worth of palpitations that have increased in frequency. Her symptoms are not associated with chest pain, syncope, dyspnea, or dizziness. She has no pertinent past medical history. She has the potential triggers of caffeine consumption, diet pill use, and stress. Family history of heart disease also noted. Her examination is normal.

- **Most likely diagnosis:** Cardiac dysrhythmia, benign.
- **Next diagnostic step:** Obtain 12-lead ECG.
- **Next step in therapy:** Restrict caffeine, alcohol, and drugs (especially amphetamine-based stimulants and diuretics) for next 2 weeks; keep a diary of symptoms or possible triggers; follow-up with patient in 2 weeks. If symptoms persist, additional workup may be required.

ANALYSIS

Objectives

1. Define palpitations.
2. Identify benign rhythm disturbances and those associated with sudden cardiac death.
3. Identify the most common structural heart diseases associated with sudden cardiac death.
4. Develop a rational approach that takes into account cardiac and noncardiac causes for palpitations.

Considerations

This 35-year-old woman gives a history of frequent palpitations and otherwise appears healthy (normal physical examination) without associated dizziness or syncope. Because she is also younger than the age of 50 years (thus at low risk for coronary artery disease), she is most likely to have a nonthreatening cause for her symptoms and can be workedup on an outpatient basis.

This history is the most important part of the workup. We are given clues to noncardiac factors that may contribute to palpitations, including caffeine consumption, use of diet pills, job-related stress, and possibly stress surrounding her father's own health problems. Anemia should be considered if there is a history of fatigue, light-headedness, GI blood loss, or menorrhagia.

Family history can be very important because some dysrhythmias, such as familial prolonged QT syndrome, can run in families. A family history of premature cardiac death (or unexplained sudden death) should be sought, as hypertrophic cardiomyopathy is autosomal dominant and may not demonstrate a heart murmur when examined.

If this woman were to have a midsystolic click associated with or without a late systolic murmur, we would need to consider the presence of **mitral valve prolapse** (MVP) syndrome. Usually asymptomatic, it is the **most common valvular heart defect** in the United States, occurring in 3% to 6% of the population. Because MVP is common, the presence of palpitations may or may not be the result of this condition. Still, people may present with palpitations, fatigue, chest discomfort (not typical of angina), and dyspnea with this valvular finding. This symptom complex is defined as mitral valve prolapse syndrome. These patients may also present with panic attacks or manic-depressive syndromes. Two percent of MVP patients will have complications resulting in progression to mitral regurgitation with subsequent left-sided two-chamber enlargement, atrial fibrillation (if left atrium becomes enlarged), left ventricular dysfunction leading to heart failure, pulmonary hypertension, and infective endocarditis. For these reasons, a two-dimensional echocardiogram is recommended at least once when MVP is identified.

APPROACH TO Palpitations

DEFINITION

PALPITATIONS: A subjective sensation of unduly strong, slow, rapid, or irregular heart beats that may be related to cardiac arrhythmias. The sensation may last seconds, minutes, hours, or days. They are common and usually not dangerous. They usually are the result of a change in the heart's electrical system.

CLINICAL APPROACH

Etiologies

Approximately 40% of patients complaining of palpitations have a primary rhythm disturbance. An underlying mental health problem (anxiety or panic disorder) is the cause in 31% of symptomatic patients. Drugs (prescription, recreational, or over-the-counter) cause 6% of palpitations; intrinsic structural problems with the heart are the cause of 3%; 4% have noncardiac causes; and the remaining 16% have no identifiable cause.

The largest group has some type of primary rhythm disorder, including sinus bradycardia, sinus tachycardia, Wolf-Parkinson-White (WPW) syndrome, sick sinus syndrome, premature atrial contractions, supraventricular tachycardias, premature ventricular contractions, and ventricular tachycardia. These rhythm disturbances can be seen in childhood and adulthood.

Supraventricular tachycardia is caused by a cardiac source of the arrhythmia that is not in the ventricle. This category includes atrial fibrillation, atrial flutter, focal atrial tachycardia, multifocal atrial tachycardia (MAT), and AV nodal reentrant tachycardia. Atrial fibrillation is the most common of all the arrhythmias and becomes increasingly more common with older age and cardiomyopathy. MAT is classically found in the presence of COPD.

WPW syndrome is caused by an accessory track between the atria and ventricles that conducts electrical impulses in addition to the AV node. The classic ECG finding is a slurring on the upstroke of the QRS complex known as a delta wave. WPW can cause dangerous arrhythmias and lead to sudden cardiac death. Brugada syndrome is an ion channel disorder that is most common in Asian males. On an ECG, it presents as ST-segment elevation in leads V_1 to V_3, and it too can cause dangerous arrhythmias that result in death.

Sick sinus syndrome usually involves a dysfunction of the SA node that leads to bradycardia and can cause fatigue and syncope. Patients, however, can also have a tachycardia-bradycardia variety of sick sinus syndrome in which they also experience supraventricular tachycardia with its associated symptoms of palpitations and angina pectoris.

Patients with **long QT interval syndrome** are at increased risk for ventricular arrhythmias and sudden cardiac death (SCD). Long QT syndrome is caused by mutations in multiple genes and can have an **autosomal dominant pattern.** It is seen more commonly in females. Patients with this syndrome will present with either palpitations and/or syncope and have a family history of syncope or sudden death. Prolonged QT interval is defined as QT_C* 470 msec in men or greater than 480 msec in women. **Any patient with a QT interval greater than 500 msec is at increased risk for dangerous dysrhythmias.** Prolonged QT intervals may also be the result of the use of certain medications such as quinidine, procainamide, sotalol, amiodarone, and tricyclic antidepressants.

Benign rhythm disturbances include premature atrial contractions, sinus tachycardia, and sinus bradycardia appropriate for activity/stress level, sinus pauses less than 3 seconds and isolated unifocal premature ventricular contractions (PVCs). However, PVCs in the presence of known cardiac disease,

*QTC is defined as measured QT interval corrected for heart rate:

$$QT_C = \frac{QT(\text{in msec})}{\sqrt{RR\ \text{interval (in msec)}}}$$

metabolic disease, or the presence of worrisome symptoms (such as near syncope, syncope, or seizures) require aggressive workup because of the risk of ventricular tachycardia or fibrillation. PVCs occurring at rest and disappearing with exercise are usually benign, commonly seen in athletes, and require no investigation.

Psychiatric causes are always considered in the differential diagnosis for palpitations and may be missed if not screened for in the initial history. Panic disorder is seen more often in women of childbearing age. Patients with panic attacks commonly present to emergency departments. They will report brief episodes of overwhelming panic or sense of impending doom associated with tachycardia, dyspnea, or dizziness. Still, these complaints may be identical to primary rhythm disturbances and deserve formal workup.

Cardiac or structural problems include cardiomyopathy, atrial or ventricular septal defects, congenital heart disease, mitral valve prolapse, pericarditis, valvular heart disease (eg, aortic stenosis, aortic insufficiency), and congestive heart failure. The presence of restrictive, hypertrophic, or dilated cardiomyopathies may lead to sudden cardiac death.

Hypertrophic cardiomyopathy is the most common cause of sudden cardiac death in adolescents in the United States. These patients may present with chest pain, syncope, and palpitations. Hypertrophic cardiomyopathy may be passed down as an autosomal dominant trait. A heart murmur, if present, will usually be systolic and will be accentuated by Valsalva maneuver. Echocardiography demonstrating a thickened intraventricular septum remains the gold standard for diagnosis.

Marfan syndrome should be suspected in patients who are tall and have scoliosis, pectus excavatum, long, thin digits (arachnodactyly), high-arched palate, and an arm span exceeding their height. Mitral valve prolapse may be seen in patients with Marfan syndrome. These patients often have aortic root dilations and are at risk for aortic arch aneurysm rupture. The diagnosis can be confirmed by echocardiography.

Noncardiac causes of palpitations may be suggested by the history and examination. Noncardiac etiologies include anemia, electrolyte disturbances, hyperthyroidism, hypothyroidism, hypoglycemia, hypovolemia, fever, pheochromocytoma, pulmonary disease, and vasovagal syncope. **Laboratory screening includes a complete blood (CBC), chemistry panel, and thyroid-stimulating hormone (TSH).** If a pheochromocytoma is suspected, a 24-hour urine collection for catecholamines and metanephrines is required.

Numerous medications and substances may contribute to palpitations. Among these are alcohol, caffeine, street drugs (cocaine), tobacco, decongestants (often found in OTC and herbal weight loss drugs), diuretics (causing electrolyte disturbances), digoxin, β-agonists (eg, albuterol), theophylline, and phenothiazine. Patients should be questioned about their use of over-the-counter medications, herbs, and supplements, as they often will not provide this information unless specifically asked.

CLINICAL PRESENTATION

Evaluation of a patient presenting with palpitations should take into account numerous factors. The patient's age at symptom onset is important, as an **age older than 50 years should always lead to the consideration of coronary artery disease.** Possible triggers should be pursued, such as medication use, exercise, and stress. Pay particular attention to palpitations associated with syncope, as these are usually pathologic and hospitalization should be considered.

The clinical examination should focus on vital signs (blood pressure and heart rate), including orthostatic readings if suggested by history. The thyroid gland should be examined for abnormalities such as goiter, nodule, or bruit. The presence of resting tremor or brisk reflexes should also lead one to consider hyperthyroidism.

The cardiac examination should be thorough. The point of maximum impulse should be palpated, as displacement may suggest cardiomegaly. The rate and rhythm should be noted, particularly if there are any irregularities. For example, an irregularly irregular rhythm is suggestive of atrial fibrillation whereas an occasional extra beat may be PVCs. Extra sounds, such as the midsystolic click of mitral valve prolapse or any murmurs consistent with valvular pathology, should also be documented.

A 12-lead electrocardiogram is appropriate in all patients with palpitations, even if they are symptom free during physician encounter. The presence of left ventricular hypertrophy, atrial enlargement, atrioventricular block, old myocardial infarction, and delta waves (as seen in WPW syndrome) should trigger additional testing. Prolonged QT intervals increase the risk for dangerous rhythm disturbances and usually require consultation with a cardiologist or cardiac electrophysiologist.

Other cardiac testing may be appropriate based on the history, examination, and results of the initial evaluation. **Ambulatory electrocardiographic rhythm monitoring** can be accomplished **for periods of 24 to 72 hours using a Holter monitor**. A cardiac **event monitor can be worn by a patient for up to 30 days** and might be useful when the palpitations do not occur daily. The monitor is worn continuously and activated by the patient when palpitations are felt.

An echocardiogram might be useful in identifying patients with suspected structural abnormalities of their heart chambers or heart valves, which could trigger heart rhythm disturbances. These findings could be missed on physical examination. A transesophageal echocardiogram may be performed to look for a thrombus prior to cardioversion. Exercise stress tests in age-appropriate patients may be important for identifying dysrhythmias triggered by exercise. This may be of particular importance in patients with suspected coronary artery disease. Anyone with suspected structural problems should be evaluated by an echocardiogram before undergoing exercise. Patients with suspected hypertrophic cardiomyopathy or severe aortic stenosis should avoid exercise stress testing, as they may develop heart rhythm disturbances which may be

nonrecoverable. Finally, electrophysiology studies may be needed to recreate rhythm disturbances and identify hyperactive foci and accessory tracts such seen in WPW syndrome. These areas can subsequently be electrically ablated.

TREATMENT

The treatment of a given patient's symptoms is dependent on the etiology. If medication related, the offending agent should be stopped. Anxiety may be treated by a combination of pharmacologic and nonpharmacologic interventions. If the problem is structural cardiac disease, referral to a cardiologist is usually indicated.

Primary supraventricular rhythm disturbances may respond nicely to β-blockers or calcium channel blockers. Digoxin can be used to slow down rapid ventricular responses to atrial fibrillation and flutter. If symptoms are short-lived or episodic, short-acting negative chronotropics, such as short-acting β-blockers, can be used on an as-needed basis.

Symptomatic supraventricular tachycardia (SVT) can often be self-treated by patients with recurrent episodes by several vagal stimulation techniques. Carotid sinus massage, Valsalva maneuver, and cold applications to the face (diver's reflex) can trigger vagus nerve stimulation, which may break an episode of SVT. When these are unsuccessful, IV adenosine is often administered. If the adenosine terminates the SVT, then the arrhythmia is most likely a reentry SVT. If it does not, then the rate may be slowed down with β-blockers or calcium channel blockers. At that point, consultation with a cardiologist should be sought.

Chronic atrial fibrillation should be treated with medication to keep the ventricular rate below 100 bpm; these agents are often β-blockers or calcium channel blockers. **Most patients with atrial fibrillation will also require anticoagulation with warfarin,** as they are at an increased risk of embolic stroke from blood clots that form in the cardiac atrium. Both electrical and pharmacologic cardioversion of atrial fibrillation may be attempted in order to convert to a normal sinus rhythm. A transesophageal echocardiogram (TEE) should be done prior to cardioversion in order to rule out the presence of a thrombus that might dislodge with the cardioversion. If the patient converts spontaneously or with cardioversion, normal sinus rhythm may then be sustained by antiarrhythmic drugs, such as amiodarone, sotalol or with class 1C drugs such as flecainide and propafenone. Class 1C drugs should not be used in the presence of structural cardiac disease or cardiac hypertrophy.

Ventricular arrhythmias can be extremely dangerous and usually require prompt treatment. Ventricular fibrillation is not compatible with life and needs to be treated immediately with electrical defibrillation. Patients with ventricular tachycardia, who are unstable, need to be electrically cardioverted. Amiodarone should be given to a patient with stable ventricular tachycardia and in patients who were converted back into a sinus rhythm through cardioversion. Lidocaine

should be used in place of amiodarone in patients who are allergic to iodine. The most common cause of ventricular arrhythmias is ischemia.

An implanted cardioverter-defibrillator is indicated in patients with conditions that commonly result in ventricular fibrillation or tachycardia leading to sudden death. Some of these conditions are advanced dilated cardiomyopathy, long QT syndrome, hypertrophic cardiomyopathy, and Brugada syndrome.

Comprehension Questions

42.1 A 35-year-old man who has never had a physical examination comes to clinic. He recently moved to the area and needs to establish a new physician. He has had no previous medical problems to date and no pertinent family history. He denies any changes in bowel or bladder habits and does not smoke or drink. When prompted he says that he has noticed a "fluttering" in his chest for past 3 months that spontaneously resolves. He has had increased stress at work and has been drinking six cups of coffee a day to complete his workload. He has not had time to exercise and his diet consists of what he can find in the office cafeteria. He denies any history of anxiety. Which of the following is the most common cause of underlying etiology of palpitations?

A. Medication
B. Structural heart disease
C. Coronary artery disease
D. Primary rhythm disturbance
E. Idiopathic

42.2 A 42-year-old asymptomatic woman is noted to have an abnormal finding on ECG. Which of the following is an indication for referral to a cardiologist or cardiac electrophysiologist?

A. PVCs on a resting ECG that resolve with exercise
B. Delta waves on an ECG
C. Isolated unifocal PVCs found on ECG
D. Sinus arrhythmia

42.3 Which of the following patients should undergo an exercise stress test for evaluation of his condition?

A. A 60-year-old with symptomatic PVCs
B. A 35-year-old with hypertrophic cardiomyopathy seen on an echocardiogram
C. A 32-year-old, tall, slender man with pectus excavatum and mitral valve prolapse on examination
D. A 68-year-old with suspected aortic stenosis

42.4 A 16-year-old adolescent male comes to the office for a sports physical. He is planning to try out for his high school football team but first needs medical clearance. He has no complaints and his history is unremarkable, except for a family history which includes an uncle dying suddenly while jogging at age 25. His physical examination is unremarkable except for a harsh systolic murmur loudest over his left lower sternal border. You get an ECG which shows left ventricular hypertrophy. Which of the following is the most appropriate next step in management?

A. An exercise stress test
B. An echocardiogram
C. A chest x-ray
D. A coronary catheterization
E. Reassurance that he is fit to play football

42.5 You are called to the bed side of a patient who was complaining of chest pain. When you get there you find the patient confused and not answering questions. The nurse informs you that the patient was speaking coherently only a moment before. The patient's pulse is 180 bpm, his systolic blood pressure is 60 mm Hg, and his diastolic cannot be measured. He was admitted to the hospital for a condition completely unrelated to chest pain. A rhythm strip shows ventricular tachycardia. Which of the following is the most appropriate next step in the management of this patient?

A. Adenosine
B. Cardiology Consultation
C. Emergent electrical cardioversion
D. Negative chronotropic agent
E. 12-lead ECG

ANSWERS

42.1 **D.** Primary rhythm disturbances are the most common cause of palpitations, making up approximately 40% of cases. Other common causes include anxiety, medications, and structural heart disease. Many cases of palpitations remain undiagnosed in spite of appropriate evaluation.

42.2 **B.** The presence of delta waves indicates WPW syndrome and the presence of an accessory tract that can be ablated by an electrophysiologist.

42.3 **A.** A 60-year-old with PVCs, especially if they are of new onset, may be showing the initial presentation of coronary artery disease and should undergo stress testing. All of the other conditions listed are contraindications to stress testing.

42.4 **B.** This young man has signs suggestive of hypertrophic cardiomyopathy. The confirmatory test for it is an echocardiogram. Coronary catheterization and stress testing are tests for coronary artery disease and not recommended for this patient. A β-blocker or calcium channel blocker would worsen the patient's hemodynamic status. Adenosine is indicated for supraventricular tachycardia with a narrow QRS complex and not ventricular tachycardia.

42.5 **C.** This patient has ventricular tachycardia with clinical deterioration and hemodynamic instability. He needs immediate electrical cardioversion.

Clinical Pearls

- Consider Marfan syndrome in a tall patient with long arms, long fingers, who wears glasses.
- A 24- to 72-hour Holter monitor is appropriate in a patient with frequent (ie, daily) palpitations; a 30-day event monitor is a better test in someone with infrequent episodes.
- Hypertrophic cardiomyopathy is the most common cause of sudden cardiac death in adolescents. An adolescent with a systolic heart murmur that increases in intensity with Valsalva maneuver should have his/her activity restricted until a diagnostic echocardiogram can be performed.

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Case 43

The mother of a 16-year-old girl calls you when you are on call on a Saturday afternoon. The mother states that her daughter was stung by a wasp about 2 hours ago on her left arm. The patient has no known history of previous allergic reactions to insect bites or stings. She is having no difficulty breathing or swallowing, nor has she been dizzy or lightheaded. The mother's primary concern is that the area of the sting is red and swollen. The daughter says that it hurts and itches. She says that the site of the injury was the midpoint of the forearm and there is now redness and swelling extending in a circular pattern that is about 3 in across. The red area is hot to the touch, so the mother is concerned that it is infected. She gave her daughter some ibuprofen for the pain and would like you to phone in some antibiotic and something to prevent the reaction from spreading.

- Which antibiotic should you prescribe to treat this condition?
- What other treatments might be beneficial at this point?
- What immunization is appropriate for this patient?

ANSWERS TO CASE 43:
Sting and Bite Injuries

Summary: A 16-year-old adolescent female has been stung by a wasp and is having a painful, itchy local reaction. She has no history of previous allergic reactions. The patient's mother is calling and asking you to manage the situation over the phone.

- **Most appropriate antibiotic to use:** No antibiotic treatment is indicated, as this is a local reaction.
- **Other therapy that may be beneficial:** Local applications of ice, nonsteroidal anti-inflammatory drug (NSAID) or acetaminophen for pain, and antihistamine for itching.
- **Immunization that is appropriate:** Tetanus-diphtheria booster, if not up to date.

ANALYSIS

Objectives

1. Know the insects that commonly cause bite and sting injuries.
2. Be able to differentiate local from systemic reactions to bites and stings.
3. Know the management of common animal-bite injuries.

Considerations

This adolescent without allergies has received a wasp sting, and no other therapy is needed other than symptomatic treatment. The insect order Hymenoptera includes wasps, yellow jackets, hornets, honeybees, bumblebees, and fire ants. These insects cause the majority of cases of sting- or bite-induced anaphylaxis and cause more mortality than all other types of insect bites and stings. Local reactions occur as a result of the toxic properties of the venom, whereas more severe reactions tend to be caused by allergic reaction to venom allergens.

Several types of bee stings result in retention of the stinger in the victim, which can result in continued injection of the bee venom. Stingers should be promptly removed. Grasping the base of the stinger may result in compression of a venom-containing sac, resulting in increased venom release. Thus it is suggested that scraping or brushing the stinger off of the skin is preferable to grasping the stinger. However, **rapidly removing the stinger is preferable to taking the time to locate a scraping implement** if one (such as a credit card or driver's license) is not immediately at hand.

APPROACH TO
Bites and Stings

DEFINITIONS

HYMENOPTERA: Order of insects which includes wasps, yellow jackets, hornets, honeybees, bumblebees, and fire ants, and make up the majority of insect stings.

LARGE LOCAL ALLERGIC REACTIONS: Redness or warmth of the skin at the area of insect sting, mediated by immunoglobulin (Ig) E reactive to the hymenoptera venom.

CLINICAL APPROACH

INSECT STINGS

Local Reactions

Almost all Hymenoptera stings will result in a **local reaction**, which includes redness, swelling, pain, and itching at the site of the injury. These reactions **tend to occur almost immediately and last for a few hours.** The local tissue response is a consequence of a histamine-like reaction caused by the venom that is released by the sting. Local reactions can be treated with ice and antihistamines for itching. Tetanus prophylaxis should be provided for those who have not been vaccinated.

Delayed Reactions

Large local allergic reactions are mediated by immunoglobulin (Ig) E reactive to the hymenoptera venom. These reactions are often confused with cellulitis, as large areas (≥ 10 cm in diameter) of redness and warmth develop over 24 to 48 hours. These reactions are not infectious and will not respond to antibiotics. These reactions are **best treated with oral steroids** initiated early after the sting. Tetanus prophylaxis should be reviewed and updated, if needed. A person with a history of a large local reaction to a bee sting is likely to have similar reactions to subsequent stings. However, the history of this type of reaction does not result in an increased risk of anaphylaxis to subsequent stings.

Anaphylaxis

Up to 4% of the population may have a systemic reaction to a hymenoptera sting. Those who have had a systemic reaction have a 50% or greater risk of

having a systemic reaction to future stings. These systemic reactions can vary from milder symptoms of nausea, generalized urticaria, or angioedema to severe and life-threatening hypotension, shock, and airway edema. Severe immediate-hypersensitivity reactions usually occur within minutes of the sting.

Treatment of anaphylaxis should include assessment and management of the ABCs (airway, breathing, and circulation), with intubation, if necessary, IV access, and fluid resuscitation at 10 to 20 mg/kg (usually 500-1000 cc) as soon as possible. **Subcutaneous or intramuscular injection of 0.3 to 0.5 mL of 1:1000 solution of epinephrine should be given as quickly as possible** and repeated in 10 to 15 minutes if needed. Antihistamines, steroids (if severe), and bronchodilators may be required as well. Anyone with an anaphylactic reaction should be observed in a hospital setting for 12 to 24 hours, as the symptoms can recur. Persons with known anaphylactic reactions should be prescribed epinephrine injector kits to carry with them for immediate access at all times. They should be instructed to avoid wearing perfumes, bright clothing, and avoid walking barefoot. Desensitization therapy can also be offered to those with known anaphylaxis, as their risk of future severe reactions can be reduced by up to 50%.

ANIMAL BITES

Nearly five million animal bites occur in the United States each year. The most common animals involved are dogs, cats, and humans.

The initial management should focus, as always, on the ABCs and on protection of the current injury (splinting of fractures, protection of cervical spine, etc), as well as control of bleeding and assessment of the injuries incurred. History should be gathered on the type of animal involved in the bite, the situation regarding the bite (whether provoked or unprovoked), and the vaccination status of the animal, particularly to document rabies vaccination status. Almost all cases of human rabies in the United States since 1960 have been caused by bats, skunks, dogs, and foxes. Consultation with your local health department after animal bites is recommended.

Local cleaning of the wound(s) with soap and water, irrigation with saline, and debridement of devitalized tissue should take place as soon as possible. Often, for minor wounds, these treatments are all that is needed.

The risk of infection is dependent on numerous factors. Larger and deeper wounds are more likely to become infected than smaller, superficial wounds. Hand wounds also tend to have an increased risk of infection. Host factors, such as the presence of chronic illnesses or immune suppression, also play a role. The animal involved in the bite is important. Approximately 20% of dog-bite wounds become infected, whereas cat and human bites have a higher occurrence of infection.

Many different bacteria can be involved in bite wound infections. Both cats and dogs can carry staphylococci, streptococci, anaerobic species, and

Pasteurella species. Humans carry staphylococci, streptococci, *Haemophilus* species, *Eikenella* species, and anaerobes.

The treatment of bite wounds starts with local care—cleaning, irrigation, and debridement. The primary closure of bite wounds is controversial and should be limited to lacerations less than 24 hours old. Deep puncture and wounds with signs of infection should not be primarily closed. Tetanus vaccination should be updated in those patients as needed. Animal control authorities should be contacted for guidance regarding rabies vaccination.

Although clear evidence of efficacy is lacking for dog and cat bites, current recommendations are for antibiotic prophylaxis for 5 to 7 days for patients with moderate to severe wounds from dog, cat, or human bites. Amoxicillin-clavulanate (Augmentin) given orally is an appropriate prophylaxis for most bite wounds. When cellulitis is present, longer courses of antibiotic, usually 7 to 14 days, are required. Hospitalization and surgical intervention may be required for more severe infections, osteomyelitis, joint infections, and in patients with complicating medical conditions.

Comprehension Questions

43.1 Which of the following therapeutic options is useful in treating of both bee stings and bite wounds?

A. Antibiotic prophylaxis with amoxicillin-clavulanate
B. Antihistamines for itching
C. Tetanus vaccination
D. Surgical wound debridement

43.2 A 22-year-old woman develops a progressively enlarging red, hot area on her leg following a yellow jacket sting. She states that the sting was sharp and of brief duration and she was able to fully remove the stinger with tweezers. She did not suffer from any systemic anaphylaxis. She has no previously known allergies. She sees you in the office a day after the sting and says that the lesion is still enlarging despite using over-the-counter corticosteroid cream and a first-generation antihistamine. Which of the following is the most appropriate treatment for this patient?

A. Oral prednisone
B. Topical corticosteroid
C. Antibiotic directed against gram positive cocci
D. Portable epinephrine kit for future stings
E. Reassurance

43.3 You see a 7-year-old boy a day after he was bitten by his pet dog. According to the mother, the dog bit the child after he snuck up on the dog and grabbed its tail. The dog has had all its vaccinations, including rabies. The child has had no fever, has full movement of the injured limb, and has no sign of neurologic or vascular injury. The wound is on the child's forearm, is not deep, and is not bleeding, but has developed about 2 cm of erythema surrounding the site. Which of the following is the most appropriate treatment?

A. Hospitalization for IV antibiotic
B. Oral amoxicillin-clavulanate for 3 to 5 days
C. Oral amoxicillin-clavulanate for 7 to 14 days
D. Local care without any antibiotic

43.4 You see a 43-year-old man who 2 days prior was in a fist fight and sustained a deep laceration wound around the knuckles from where he struck the face of another man. He was intoxicated at the time and upon return home he did not clean the wound and went straight to sleep. He now has purulent drainage, pain, erythema, and fever. There is no rash and he has not noted any spreading of the erythema. An x-ray of the hand shows a hairline fracture of the fifth metacarpal with swelling and bruising noted over the affected area. Which of the following is the most likely organism causing infection?

A. *Staphylococcus aureus*
B. Streptococci
C. *Eikenella corrodens*
D. *Escherichia coli*
E. *Peptostreptococcus*

43.5 A mother brings in her 6-year-old child who was bitten on the hand while playing with a rabbit that was recently obtained from a neighbor. The child's wound is on the volar surface of the right second finger just distal to the proximal interphalangeal joint. Which of the following steps in the management of bite wounds is most effective in preventing wound infection?

A. Tetanus prophylaxis
B. Rabies prophylaxis
C. Saline irrigation and wound care
D. Prophylactic antibiotics
E. Irrigation and primary closure

ANSWERS

43.1 **C.** Tetanus vaccination is common to the management of both bee stings and bite wounds. Bee stings rarely become infected and do not require antibiotic therapy.

43.2 **A.** This patient is having a large, local reaction to her sting. This is an IgE-mediated reaction. It may respond to a course of oral steroids. There is at least a 50% chance that a similar reaction will occur if she were stung again, but she is unlikely to develop anaphylactic reactions in the future and does not need anaphylaxis prophylaxis. Her history of sting makes cellulitis less likely.

43.3 **C.** This child is developing cellulitis from the bite wound. Based on his presentation, he does not appear to require hospitalization. He can be treated with oral antibiotics for 1 to 2 weeks.

43.4 **C.** While each of these bacteria can be isolated in injuries from human bites, *Eikenella* species appear to be most common in closed fist injuries.

43.5 **C.** Rodents and lagomorphs (rabbits) are neither reservoirs of the rabies virus nor have been shown to transmit the rabies virus to humans. The most important step in preventing the infectious complications of bite wounds is proper wound care with inspection, irrigation, and debridement. Tetanus prophylaxis should be considered in all bite wounds. Antibiotic prophylaxis may also be indicated especially in high-risk bites (those located on the hand, late presentation, cat bites) and should be directed against staphylococci, streptococci, anaerobes, and *Pasteurella* species as appropriate.

Clinical Pearls

- Anyone with a history of anaphylactic reactions should be given a prescription for an epinephrine injector kit and instructed in the importance of keeping it at hand. These prescriptions need to be updated often, as the medication expires in 6 to 12 months.
- Human "bite" wounds are not always the result of a bite. A punch to the mouth can cause a serious inoculation and infection to the knuckles of the puncher.

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Case 44

A 60-year-old man is brought to the emergency room by ambulance because of slurred speech and left-side weakness. His wife states the patient went to bed approximately at 11 PM the night before and was well. At 5 AM, the time they usually get up, she noticed that he had some difficulties talking and moving his left arm and leg. They arrived at the emergency department at 6 AM. He has history of long-standing hypertension (HTN), heart attack 10 years before, and high cholesterol. He is taking baby aspirin, an angiotensin-converting enzyme (ACE) inhibitor, and a statin on a daily basis. He heavily consumed alcohol in the past, but stopped after the heart attack. He still smokes a half pack of cigarettes daily. His wife remembers that about 3 months ago he complained of mild bilateral leg pain during their morning walk and had to stop after 15 minutes. Also, she remembers that 1 month ago he had "slight right eye blackout" for 5 minutes. On presentation to the emergency department his blood pressure is 195/118 mm Hg, his pulse is 106 bpm, his respiratory rate is 18 breaths per minute, his temperature is 99.8°F (37.6°C), and his oxygen saturation is 97% on room air. Although his pupils are equal and reactive and the ocular movements are intact, he is unable to turn his eyes voluntarily toward the left side. The neck is supple, there is no jugular venous distension, and there are no bruits. The lungs are clear, the heart sounds regular without murmurs, and the abdomen is normal. The limbs are not well-perfused distally. The neurologic examination reveals that he is alert and oriented, although he does not recognize he is sick. He is right-handed. He shows loss of awareness and attention with respect to objects or stimuli on his left side. He has mild dysarthria, but his speech is fluent and he understands and follows commands very well. There is mild weakness on the left side of the face and left-sided homonymous hemianopsia, but there is no nystagmus or ptosis, and no tongue or uvula deviation. He is not able to move his left arm and leg, has hyperreflexia, and the left great toe is upgoing.

- What is the most likely diagnosis?
- What is your next diagnostic step?
- What is your next step in therapy?

ANSWERS TO CASE 44:
Cerebrovascular Accident/Transient Ischemic Attack

Summary: The patient is a 60-year-old, right-handed man with history of coronary artery disease, hypertension, and hypercholesterolemia, who presents to the emergency room with a 5-hour history of slurred speech and an inability to move his left arm and leg. He had an episode of amaurosis fugax (blindness) in his right eye 1 month before admission. On physical examination, although he is alert and oriented, he has no awareness of his disability (anosognosia) and exhibits left-sided neglect. He has hypertension, dysarthria, and left hemiparesis. He also has left-sided homonymous hemianopsia, conjugate rightward gaze deviation, left hemifacial weakness, and left hyperreflexia.

- **Most likely diagnosis:** Cerebrovascular accident (CVA).
- **Next diagnostic step:** Obtain a brain computed tomography (CT) scan without contrast.
- **Next step in therapy:** Determine advisability for acute treatment with thrombolytic agents.

ANALYSIS

Objectives

1. Recognize the significance of a correct diagnosis and evaluation of transient ischemic attacks (TIAs) and cerebrovascular accidents (CVAs).
2. Recognize the conditions that can mimic a stroke.
3. Understand that the clinical evaluation gives the most important clues about diagnosis of stroke.
4. Be familiar with the accepted approach for the early management of patients with ischemic stroke.
5. Be familiar with the current strategies for prevention of ischemic stroke and TIA.

Considerations

This 60-year-old patient has developed focal neurologic deficits, which is the usual presentation of patients with strokes. Considering that he has a history of hypertension, hypercholesterolemia, and vascular manifestations of atherosclerosis, such as coronary artery disease and peripheral vascular disease (lower extremity claudication), ischemic stroke is the most probable diagnosis. Furthermore, he had a TIA (amaurosis fugax) 30 days before admission, which put him at even greater risk for an ischemic stroke. His neurologic

deficits are compatible with an ischemic stroke in the territory of the right middle cerebral artery, which is his nondominant hemisphere and the reason he is not aphasic.

Of immediate importance, the clinician should confirm that the neurologic impairments are secondary to ischemic stroke and not other conditions, especially intracranial hemorrhage. A brain CT without contrast should be obtained as soon as possible to exclude hemorrhage, tumor, and abscess. Blood sugar, drug screen, coagulation studies, serum electrolytes, renal function tests, lipid profile, and a complete blood count are also indicated. A cardiac monitor should be attached and a 12-lead ECG obtained so as to exclude acute myocardial infarction or atrial fibrillation.

Because it has been more than 3 hours from the onset of symptoms, this patient is not a candidate for thrombolytic therapy. The initial ABC (airway, breathing, and circulation) survey should guide treatment if the vital signs are compromised. Although his blood pressure is elevated, in the setting of an acute CVA, blood pressure management should be cautious. The patient should be admitted to the hospital for further evaluation and management, preferably to a dedicated stroke unit if available. Aspirin should be given within 48 hours of the stroke, and deep venous thrombosis prophylaxis should be used. However, anticoagulation with heparin or warfarin for the infarction itself has a poor risk-benefit ratio and is not indicated. An evaluation of his swallowing function and an early physiotherapy consultation should be obtained. Further imaging with brain magnetic resonance imaging (MRI), magnetic resonance angiography, or CT angiography can help to clarify the etiology of the stroke and guide treatment. In this patient, carotid Doppler studies are indicated as he had an episode of amaurosis fugax, which is caused by a blockage of the opthalmic artery which branches from the internal carotid.

Management of his chronic medical conditions, to try to reduce his risk of subsequent strokes, is critical. In this patient, these measures include tight control of his hypertension and hypercholesterolemia, along with smoking cessation. Because this patient had a stroke while taking aspirin, an alternative antiplatelet agent should be considered.

APPROACH TO CVA/TIA

DEFINITIONS

TRANSIENT ISCHEMIC ATTACK (TIA): A focal neurologic deficit lasting less than 24 hours.

RESIDUAL ISCHEMIC NEUROLOGIC DEFICIT (RIND): A neurologic deficit of greater than 24 hours and less than 3 weeks.

CLINICAL APPROACH

There are 700,000 people that suffer from stroke in the United States each year, and the incidence of TIA is approximately 200,000 to 500,000 per year. Strokes remain the third leading cause of death in North America and are a major cause of disability. **TIA is defined as a focal neurologic deficit lasting less than 24 hours.** Most TIAs last for less than 1 hour. A stroke is presumed to have occurred if the symptoms persist for more than 24 hours. A residual ischemic neurologic deficit **(RIND)** is defined as a neurologic deficit of greater than 24 hours and less than 3 weeks**.**

Patients with a TIA are at increased risk of a subsequent stroke. The reported occurrence of a stroke after a TIA is as high as 5.3% within 2 days and 10.5% within 90 days. Patients with a TIA often require hospital admission, further evaluation, and the same long-term management as stroke patients.

Hypertension is the single most important risk factor for stroke, and the incidence of stroke in the United States has decreased partly as a result of better efforts to control hypertension in the past few decades. Other risk factors include diabetes mellitus, older age, male sex, family history, dyslipidemia, and smoking (See Table 44–1). Many cardiovascular conditions also predispose people to stroke, usually through an embolic clot. These conditions include atrial fibrillation, myocardial infarction, endocarditis, carotid stenosis, rheumatic heart disease, presence of mechanical valve, advanced dilated cardiomyopathy, and a patent foramen ovale or atrial septal defect which can expose the systemic arterial system to a paradoxical embolus from a venous source. Sickle cell disease is also a risk factor for stroke. Patients with sickle cell commonly experience their strokes as children.

Strokes are generally classified as being of thrombotic or embolic origin. Strokes that affect the small branches of the main arteries of brain are termed lacunar infarcts or small-vessel strokes. These strokes often forewarn a larger, more debilitating stroke. The causes of the emboli are usually of cardiovascular origin and include the previously mentioned conditions as well as dissection of various vessels. Most emboli are clots. However, emboli in rare occasions can be vegetations from infective endocarditis, sterile vegetations from Libman-Sacks endocarditis (which occurs in systemic lupus erythematosus), and marantic endocarditis, which occurs with cancer.

DIAGNOSIS AND EVALUATION

Sudden onset of focal neurologic deficit is the usual presentation of stroke patients, although some patients can have a gradual worsening of symptoms. Unless there is a hemispheric infarct, basilar artery occlusion, or cerebellar stroke with edema, nearly all of the patients are alert. If the middle cerebral artery territory is affected, the patient would experience aphasia (when dominant hemisphere is involved), contralateral hemiparesis, sensory loss, spatial

Table 44–1 RISK FACTORS AND CONDITIONS ASSOCIATED WITH STROKE

Hypertension
Prior CVA
Prior TIA
Older age
Male sex
Family history
Diabetes
Hyperlipidemia
Smoking
Oral contraceptives
Hormone replacement therapy
Cocaine, amphetamine use
Coronary artery disease
Peripheral vascular disease
Carotid stenosis
Atrial fibrillation
Dilated cardiomyopathy
Recent myocardial infarction
Mechanical valve
Rheumatic heart disease
Endocarditis
Patent foramen ovale
Atrial septal defect
Nephrotic syndrome
Systemic lupus erythematosus
Homocystinemia
Antiphospholipid syndrome
Sickle cell disease
Disseminated intravascular coagulation
Malignancy
Pregnancy

neglect, and contralateral impaired conjugate gaze. When the territory of the anterior cerebral artery is affected, foot and leg deficits are more frequent than arm deficits. These patients often have associated cognitive and personality changes. Vertebrobasilar stroke symptoms and signs include motor or sensory loss in all four limbs, crossed signs, disconjugate gaze, nystagmus, dysarthria, and dysphagia. There can be ipsilateral limb ataxia and gait ataxia if the cerebellum is affected.

Assessment of the vital signs is important in the initial examination. Severe high blood pressure can be suggestive of hypertensive encephalopathy

or intracranial hemorrhage. A fever may lead to consideration of an infectious cause. A rapid or irregularly irregular pulse may imply atrial fibrillation as a potential cause of the stroke. A timely general physical examination and comprehensive neurologic examination should follow.

The differential diagnosis of acute neurologic symptoms and signs is broad. Along with CVAs, these symptoms can be caused by seizures, acute confusional states, delirium, syncope, metabolic and toxic encephalopathy (hypoglycemia), brain tumors, CNS infections, migraines, multiple sclerosis, and subdural hematoma**.** Migraines with neurological symptoms can be especially difficult to differentiate from stroke since migraines do not have to be accompanied by a headache. However, the symptoms of stroke are usually of a much more rapid onset than those of a migraine. Stroke victims are also usually alert and aware of what is happening to them, unlike people suffering from delirium or various types of encephalopathies. When it is determined that a stroke is the cause of the presentation, **it is crucial to differentiate between ischemic and hemorrhagic stroke because of the implications on further treatment.**

The initial assessment should establish if the patient is eligible for thrombolytic treatment. Establishing the time of symptom onset is the most important factor. The onset of symptoms is assumed to be the time that the patient was last known to be free of symptoms such as when they went to bed.

Brain Imaging

A CT scan of the brain without contrast is the initial imaging test of choice. CT of the brain may not show an ischemic stroke for up to 72 hours, but can exclude most cases of intracranial hemorrhage, tumors, or abscesses quickly. It is also more readily available, cost effective, and takes less time than MRI. CT scan can also be used to detect a hemorrhagic transformation of an infarct in a patient with an ischemic stroke whose symptoms deteriorate.

Further imaging studies may be indicated to clarify the etiology of the stroke and to detect intracranial or extracranial arterial occlusions, which may affect treatment decisions. Evaluation of the cerebrovascular system can be accomplished with magnetic resonance angiography (MRA), CT angiography, catheter angiography, or transcranial Doppler ultrasonography.

Other Tests

A 12-lead ECG should be done in all stroke patients in order to detect acute myocardial infarctions, which can both cause strokes or be the result of a stroke. An ECG will also aid in the diagnosis of atrial fibrillation. Echocardiography may also be necessary to adequately assess the heart. Transesophageal echocardiography is particularly useful in detecting cardiac sources of embolism, such as thrombus caused by myocardial infarction, endocarditis, rheumatic heart disease, valvular prostheses, and atrial septal defects. A carotid Doppler study is often advisable as well in order to evaluate for carotid plaques or stenosis.

Blood glucose, electrolytes, renal function tests, and drug screening are important to exclude hypoglycemia and metabolic and toxic encephalopathy. If the patient is on anticoagulant therapy, the prothrombin time, partial thromboplastin time, and platelet count should be measured and are required before considering thrombolytic therapy. A lipid panel, erythrocyte sedimentation rate, ANA, complete blood count, and serologic tests for syphilis are also oftentimes indicated. In young patients with no identifiable cause for a stroke, a workup for coagulation disorders or antiphospholipid syndrome may be indicated. A lumbar puncture is indicated if subarachnoid hemorrhage is considered and the CT is not diagnostic or if a CNS infection is possible.

TREATMENT

As in every critical patient, **the initial survey should assess the ABCs.** If hypoxia is detected, supplemental oxygen should be administered to maintain oxygen saturation above 95% and the cause of the hypoxia investigated (partial airway obstruction, aspiration pneumonia, atelectasis). An endotracheal tube should be placed if the airway is threatened. **A cardiac monitor should be placed to detect atrial fibrillation or any other arrhythmias.**

Unless a hypertensive encephalopathy, aortic dissection, acute renal failure, or pulmonary edema is present, the **treatment of arterial hypertension should be cautious.** Antihypertensive medication is recommended when the systolic blood pressure is greater than 220 mm Hg or the diastolic blood pressure is greater than 120 mm Hg. If the patient is suitable for thrombolytic treatment, medication should be initiated to decrease the systolic blood pressure to less than 185 mm Hg and the diastolic blood pressure less than 110 mm Hg. The agents most frequently used are IV labetalol, nicardipine, and sodium nitroprusside.

Fever and high blood sugar after a stroke are often associated with poorer outcomes and should be controlled during the poststroke period. An infectious source for the fever should be investigated.

Except when thrombolytic therapy is given, **most patients with a nonhemorrhagic stroke should receive aspirin within the first 48 hours**. Urgent anticoagulation is not recommended.

Judiciously selected patients can benefit from intravenous administration of recombinant tissue-type plasminogen activator (rtPA) if they can be treated within 3 hours of the onset of ischemic stroke. The risk of hemorrhage associated with rtPA treatment is approximately 5% and there are numerous contraindications to the use of thrombolytic therapy, including recent surgery, trauma, gastrointestinal bleeding, myocardial infarction, use of certain anticoagulant medications, and uncontrolled hypertension. Depending on availability, some hospitals have the capability of direct intra-arterial thrombolysis in which the thrombolytic agent is delivered directly to the clot via canalization or even mechanical retrieval of thrombus. These modes of treatment may be considered in centers with experimental protocols or extensive experience.

Poststroke cerebral edema can be a very serious complication and can lead to herniation of brain stem resulting in death. This edema can be treated with mannitol or decompression surgery, although it is insufficient evidence to show significant benefit for these treatments at this time.

Studies have shown that treatment in a dedicated stroke unit results in better outcomes and less mortality. Early posttreatment care includes mobilization once the patient is stable and evaluations of the patient's ability to swallow. After a stroke, the patient is often immobile and needs intensive medical care in order to avoid malnutrition, skin breakdown, and other complications. The patient's neural deficits usually improve after the stroke and can keep improving up to 6 months to a year. Prior strokes also predispose patients to seizures, and some patients may initially present with a seizure as the first symptom of stroke. When thrombolytic therapy is not used, deep vein thrombosis prophylaxis should be provided. Family support and treatment of depression should be also initiated when appropriate.

PREVENTION OF STROKE IN PATIENTS WITH PREVIOUS ISCHEMIC STROKE OR TIA

A history of a previous TIA or CVA confers a high risk for future events. Aggressive risk factor control should be undertaken in these patients. All patients should be counseled to quit smoking and to reduce alcohol intake. Hypertensive patients should be treated per JNC-7 (Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure, 7th report) guidelines (see Case 30). High cholesterol should be treated with a goal of low-density lipoprotein (LDL) less than 100 mg/dL. Tight diabetic control should be sought. Antiplatelet agents such as aspirin (50 to 325 mg/d), the combination of aspirin and extended-release dipyridamole (Aggrenox), or clopidogrel (Plavix) should be started in patients with a history of noncardioembolic ischemic stroke or TIA.

Carotid endarterectomy (CEA) can reduce the risk of stroke in someone with a history of previous TIA/CVA and carotid artery stenosis. It is indicated for symptomatic patients with carotid stenosis greater than 70% when it can be performed by an experienced surgeon with a low rate of perioperative complications. CEA can be considered for symptomatic patients with a 50% to 70% stenosis, but is not indicated when there is less than 50% stenosis. Noninvasive carotid balloon angioplasty and stenting is now also being done and is an alternative to CEA.

Anticoagulation with warfarin reduces the risk of stroke and stroke recurrence in certain circumstances. It is indicated to reduce the risk of embolic strokes for patients with persistent or paroxysmal atrial fibrillation or very advanced heart failure. It is also indicated for patients with an ischemic stroke caused by a myocardial infarction and existence of left ventricular thrombus, as well as for patients with rheumatic heart disease or a mechanical heart valve.

Comprehension Questions

44.1 A 72-year-old man is brought into the emergency center because of weakness and numbness of the right arm. The medical student on the case asks the attending doctor about the diagnosis and management of transient ischemic attacks. Which of the following would be expected in patients with a TIA?

A. Resolution of symptoms within one hour
B. Stroke within 90 days in less than 1% of patients
C. CT evidence of infarction
D. MRI evidence of infarction

44.2 An 84-year-old African American woman was found by her daughter-in-law walking down the street a few blocks from her house. The daughter-in-law noticed that she did not appear to know where she was and did not recognize her. Upon prompting she seemed confused and would not speak. The patient experienced a cerebrovascular accident 1 year previously and had mild residual deficits on her left side. She takes medication for hypertension, hyperlipidemia, constipation, and gout. In the emergency room the patient has a blood pressure of 145/76 mm Hg, pulse of 86 bpm, respiratory rate of 18 breaths per minute, and temperature of 97.9°F (36.6°C). She does not follow commands and is oriented to person. She complains of headache. A CT of the brain does not show evidence of a bleed. The physician suspects subarachnoid hemorrhage. Which of the following is the most appropriate next step in management?

A. Lumbar puncture
B. Chest x-ray
C. Brain CT with contrast
D. MRI of the brain

44.3 An 82-year-old man with suspected stroke is transferred to a major medical trauma center from an outside rural hospital. Four hours have elapsed since first presentation. Which of the following should be considered in the management of this patient?

A. Avoidance of acetaminophen
B. Aggressive blood pressure management
C. Thrombolysis
D. Early mobilization

44.4 A 65-year-old man was hospitalized due to weakness of the right arm, which was diagnosed as an ischemic stroke. Which of the following is the best step regarding prevention of future strokes in this patient?

A. He would likely benefit from oral anticoagulation.
B. If he has 60% right carotid occlusion, then he is likely to benefit from carotid endarterectomy.
C. Aspirin is an acceptable option for initial therapy.
D. LDL cholesterol should be treated with a goal of less than 130 mg/dL.

44.5 A man is brought to the emergency room by ambulance. Coworkers at his office stated that he was acting normally until approximately 1 hour ago when he became confused and had trouble walking. One coworker thought that his right leg seemed especially weak. The vitals are temperature 98.6°F (37°C), pulse 110 bpm, and blood pressure 120/80 mm Hg. The patient is arousable but does not follow commands. He has a medical alert bracelet on his arms indicating that he is a diabetic and allergic to penicillin. A blood glucose taken at the bedside is 20 mg/dL. Which of the following should be your immediate next step?

A. Immediately give the patient glucose or glucagon.
B. Immediately obtain a CT scan to assess possibility for giving rtPA.
C. Immediately perform a lumbar puncture to assess for meningitis.
D. Immediately give the patient mannitol.
E. Immediately start CPR with chest compressions.

ANSWERS

44.1 **A.** A TIA is a brief neurologic episode, typically less than 1 hour in duration that does not cause infarction. The occurrence of stroke after TIA is as high as 5.3% within 2 days and 10.5% within 90 days. Warfarin is indicated in specific circumstances, such as the presence of atrial fibrillation, but is not routinely used following a TIA.

44.2 **A.** Routine chest x-rays affect the clinical management in few patients with stroke, and are not recommended as routine initial workup. CT of the brain *without* contrast can exclude most cases of intracranial hemorrhage, tumors, or abscesses, and is the initial test of choice in the workup of suspected stroke but it can miss up to 15% of subarachnoid hemorrhages. When a subarachnoid hemorrhage is suspected but not seen on CT, a lumbar puncture is indicated for diagnosis.

44.3 **D.** Mobilization of stroke patients should be started when they are considered medically stable. In the setting of an acute stroke, management of high blood pressure should be cautious. Thrombolytic therapy can be beneficial in selected patients, but carries significant risks and has numerous contraindications. Fever should be treated and a workup performed to determine its etiology, as it carries an increased risk of morbidity and mortality.

44.4 **C.** Patients with stroke but no detected sources of embolism benefit from antiplatelet agents, not anticoagulants. Aspirin, clopidogrel, or a combination of aspirin and dipyridamole are acceptable regimens. For patients with recent TIA or ischemic stroke and ipsilateral severe (>70%) carotid artery stenosis, carotid endarterectomy is recommended. When the degree of stenosis is less than 50%, there is no indication for CEA. Patients with a history of symptomatic cerebrovascular disease should be treated to an LDL goal of less than 100 mg/dL.

44.5 **A.** The patient has severe hypoglycemia and needs to be treated immediately with glucose or glucagon. If the patient does not recover with glucose or glucagon infusion, then other tests, such as a CT scan, may be warranted. But the most important first step is to treat the patient's low blood sugar. Be aware that hypoglycemia can mimic many of the symptoms of a stroke, including focal weakness. Mannitol is used in cases of cerebral edema and not for raising blood sugar.

Clinical Pearls

- Hypertension is the single most important risk factor for stroke.
- Although most strokes are cerebral infarcts, it is crucial to differentiate between ischemic and hemorrhagic stroke because of the implications on further treatment.
- CT of the brain without contrast is the initial imaging test of choice in most suspected strokes.
- Unless a hypertensive encephalopathy, aortic dissection, acute renal failure, or pulmonary edema is present, the treatment of arterial hypertension should be cautious.

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Case 45

A 39-year-old homeless man presents to the emergency department for cough and fever. He says that his illness has been worsening over the past 2 weeks. He originally had dyspnea on exertion and now is short of breath at rest. On questioning, he tells you that he lives in a homeless shelter when he can, but he frequently sleeps on the streets. He has used IV drugs (primarily heroin) "on and off" for many years. He denies medical history but the only time he gets medical attention is when he comes to the emergency department for an illness or injury. On review of systems, he complains of fatigue, weight loss, and diarrhea. On examination, he is a thin, disheveled man appearing much older than his stated age. His temperature is 100.5°F (38.0°C), his blood pressure is 100/50 mm Hg, his pulse is 105 beats/min, and his respiratory rate is 24 breaths/min. His initial oxygen saturation is 89% on room air, which comes up to 94% on 4 L of oxygen by nasal cannula. Significant findings on examination include dry mucous membranes, a tachycardic but regular cardiac rhythm, a benign abdomen, and generally wasted-appearing extremities. His pulmonary examination is significant for tachypnea and fine crackles bilaterally, but no visible signs of cyanosis. His chest x-ray is read by the radiologist as having diffuse, bilateral, interstitial infiltrates that look like "ground glass."

- What is the most likely cause of this patient's current pulmonary complaints?
- What underlying illness does this patient most likely have?
- What testing and treatment should be started now?

ANSWERS TO CASE 45:
HIV and AIDS

Summary: A 39-year-old, homeless, IV drug abuser is seen with fever, cough, dyspnea, and fatigue. He is found to be tachypneic, febrile, and hypoxemic. His chest x-ray reveals bilateral interstitial infiltrates.

- **Most likely cause of current illness:** *Pneumocystis jiroveci* (formerly known as *Pneumocystis carinii*) pneumonia.
- **Most probable underlying illness:** AIDS.
- **Recommended current testing and treatment:** Complete blood count (CBC), electrolytes, arterial blood gas; HIV enzyme-linked immunosorbent assay with confirmatory Western blot; CD4 cell count; HIV RNA assay; sputum for *P jiroveci*; start treatment with trimethoprim-sulfamethoxazole (TMP-SMX) and consider starting highly active antiretroviral therapy or HAART.

ANALYSIS

Objectives

1. Know the common risks and modes of transmission of HIV/AIDS.
2. Be aware of common presentations of persons infected with HIV.
3. Learn the role of antiretroviral therapy and other adjunctive treatments in the chronic management of HIV and AIDS.
4. Be able to identify common complications and opportunistic infections associated with HIV/AIDS.

Considerations

The case described is that of a 39-year-old man who is homeless and an intravenous drug user. He has had fatigue and weight loss. He now presents with fever, tachypnea, and hypoxemia. It is likely that he is infected with HIV, and has *P jiroveci* pneumonia. Human immunodeficiency virus (HIV) infects the helper T cells of the immune system, which are defined by the presence of the cell-signaling protein CD4, and causes a decline in both their number and their effectiveness. This decline in functional helper T cells disables the cell-mediated arm of the immune system and leaves the body vulnerable to infection from multiple opportunistic organisms. This advanced stage of the HIV infection, in which such opportunistic infections occur, is known as acquired immunodeficiency syndrome or AIDS.

Pneumocystis jiroveci (formerly known as *P carinii*) pneumonia is an AIDS-defining illness in someone infected with HIV. *P jiroveci* is a fungus that may colonize many people, but typically causes disease only in those with profound

immune deficiencies, such as AIDS infections or cancers treated with chemotherapy. *P jiroveci* pneumonia usually presents with nonproductive cough, fever, and dyspnea that worsens over a few days to a few weeks. Patients usually are found to be febrile, tachypneic, and hypoxic, although their lung examination may be unremarkable (other than tachypnea). The presence of a bilateral interstitial infiltrate on chest x-ray, often described as having a ground-glass appearance, is classic for *P jiroveci* pneumonia. The identification of the organism in sputum, either spontaneously produced or induced, is diagnostic, but treatment is usually started prior to definitive diagnosis in those with a classic clinical picture.

As *P jiroveci* pneumonia occurs after the CD4 count has markedly reduced, patients often will have symptoms and signs of other AIDS-related complications as well. It is common to see oral or esophageal candidiasis, diarrhea, Kaposi sarcoma, wasting syndrome, and other complications in a patient presenting with *P jiroveci* pneumonia. Although it presents in the setting of advanced disease, *P jiroveci* pneumonia remains a common presenting illness in those who did not know that they were infected with HIV and is a frequent initial opportunistic infection in those with known HIV disease. The incidence of *P jiroveci* pneumonia is decreasing in the United States with more widespread awareness of HIV disease, broader usage of antiretroviral therapy, and prophylactic use of TMP-SMX in patients with CD4 count of less than 200 cells/μL.

APPROACH TO HIV and AIDS

DEFINITIONS

ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS): This advanced stage of the HIV infection, in which such opportunistic infections occur with specific criteria for its designation.

HUMAN IMMUNODEFICIENCY VIRUS (HIV): A retrovirus that infects the helper T cells of the immune system, which are defined by the presence of the cell-signaling protein CD4, and causes a decline in both their number and their effectiveness.

CLINICAL APPROACH

Epidemiology

Over 40 million people in the world are living with HIV infection. It is estimated that more than $2^1/_2$ million people, including over 300,000 children, die from AIDS every year with a disproportionate share of the deaths occurring in sub-Saharan Africa. HIV disease is caused by the human retroviruses, HIV-1 and HIV-2. HIV-1 is more common worldwide, whereas HIV-2 has been reported in western Africa, Europe, South America, and Canada.

In the United States, more than 1 million people are estimated to be infected with HIV, with **approximately 25% unaware of their infection.** The highest prevalence of HIV occurs in men who have sex with other men and in IV drug users, although the occurrence in heterosexual sexual contact is increasing. African Americans are disproportionately affected with infection, both in total numbers of cases and in development of new infections.

Transmission

HIV is transmitted from person to person through contact with infected blood and body fluids. Sexual contact is the most common mechanism of transmission and, while anal intercourse has the highest rate of transmission, HIV can be acquired through vaginal and oral intercourse as well. The risk of HIV transmission is also increased by the presence of genital or anal lesions caused by other sexually transmitted diseases, such as gonorrhea and genital herpes. The risk of transmission can be reduced by the proper and consistent use of latex condoms (either male or female condoms). Because HIV can pass through lambskin condoms, these are not recommended. Circumcision has also been shown to decrease the rate of HIV transmission.

Because of the large amount of undiagnosed HIV infections, the Centers for Disease Control and Prevention (CDC) in 2006 expanded screening recommendations, which are summarized in Table 45-1.

Table 45–1 HIV SCREENING RECOMMENDATIONS

For patients in all health-care settings

- HIV screening is recommended for patients in all health-care settings after the patient is notified that testing will be performed unless the patient declines (opt-out screening).
- Persons at high risk for HIV infection should be screened for HIV at least annually.
- Separate written consent for HIV testing should not be required; general consent for medical care should be considered sufficient to encompass consent for HIV testing.
- Prevention counseling should not be required with HIV diagnostic testing or as part of HIV screening programs in health-care settings.

For pregnant women

- HIV screening should be included in the routine panel of prenatal screening tests for all pregnant women.
- HIV screening is recommended after the patient is notified that testing will be performed unless the patient declines (opt-out screening).
- Separate written consent for HIV testing should not be required; general consent for medical care should be considered sufficient to encompass consent for HIV testing.
- Repeat screening in the third trimester is recommended in certain jurisdictions with elevated rates of HIV infection among pregnant women.

Reproduced from Branson BM, Handsfield HH, Lampe MA, et al. Revised recommendations for HIV testing of adults, adolescents and pregnant women in health-care settings. MMWR Recomm Rep. *2006 Sep 22; 55 (RR-14): 1-17.*

Sharing needles by IV drug users is the second most common source of transmission of HIV. Vertical transmission from an infected woman to her baby has been found to occur during pregnancy, during the process of delivery of a baby, and from breast-feeding. Blood and blood-product transfusions have been linked to infection, although the routine screening of donor blood for HIV now makes this an extremely rare event.

Health-care workers have been infected with HIV through accidental punctures with needles used on HIV-infected patients. There is also a risk of infection by infected blood entering through open skin wounds or mucous membranes. The risk of transmission to health-care workers is low and is related to the viral load of the patient, the amount of blood to which the worker is exposed, and the depth of the inoculum. Postexposure risk of developing HIV infection can be reduced by immediate and careful cleaning of the exposure/puncture site along with postexposure prophylactic (PEP) treatment with antiretroviral therapy. Post-exposure prophylaxis should ideally be started within 2 hours after the exposure and should only be used when exposure to HIV-contaminated blood is likely. Although animal models limit the usefulness of PEP to 36 hours, there is no defined time limit before starting medications. The currently recommended length of PEP is 4 weeks.

HIV has been measured in small amounts in saliva and tears of HIV-infected patients, but no cases of transmission based on exposure to these have been documented. Transmission has been reported to occur in bite wounds from infected individuals, but only when significant tissue damage and bleeding has occurred. Measurable amounts of HIV have not been found in sweat. No case of HIV has been documented to have occurred via an insect vector.

Primary Infection

Following initial exposure to HIV, some patients will complain of nonspecific symptoms, such as low-grade fever, fatigue, sore throat, or myalgias. This illness typically occurs 6 to 8 weeks following the infection and is self-limited. The primary infection is also known as acute seroconversion syndrome, as the symptoms are thought to be related to the development of antibodies to the virus.

Following the resolution of the primary infection symptoms (if any occur), there is a period of clinical latency. During this time, most infected persons are asymptomatic, although some may have lymphadenopathy. This period can last from 6 months to 10 years following the transmission of the virus. However, while the patient is asymptomatic during this period, a relentless decline in helper T-cell number and immune function usually occurs in the untreated patient, with the result that many patients initially present with profound immunodeficiency and opportunistic infections.

Clinical Categorization of HIV/AIDS Infections

The Centers for Disease Control and Prevention defines three clinical categories and three laboratory categories (based on CD4 cell count) of HIV

infection. The clinical categories are A, B, and C; and the laboratory categories are 1, 2, and 3. **For classification purposes, HIV-infected patients can be defined with both a clinical and laboratory category** (eg, A3, B2, etc).

The laboratory categories are as follows:

1. CD4 cell count of 500 cells/μL or more
2. CD4 cell count of 200 to 499 cells/μL
3. CD4 cell count of less than 200 cells/μL

Clinical **category A** includes asymptomatic HIV infection, primary HIV infection (above), and persistent generalized lymphadenopathy. Persistent generalized lymphadenopathy is defined as enlarged lymph nodes involving at least two noncontiguous sites other than inguinal nodes.

Category B infections are symptomatic conditions in an HIV-infected person that are either indicative of a defect in cell-mediated immunity or that have a course or management complicated by HIV infections. These are not AIDS-defining illnesses and were previously known as AIDS-related complex. Table 45–2 lists some of these infections, which are not AIDS-defining illnesses. Table 45–3 lists some of the **category C** conditions, which are AIDS-defining illnesses. The presence of a CD4 cell count of less than 200 cells/μL, with or without symptoms, is also considered diagnostic of AIDS.

For classification purposes, a patient's **HIV is defined by the highest clinical category in which the patient has ever qualified.** For example, someone with oral candidiasis (category B) who is treated and now asymptomatic remains in clinical category B. Similarly, once a category C condition has occurred, the person will remain in category C.

Table 45–2 SOME EXAMPLES OF HIV CLINICAL CATEGORY B CONDITIONS

Bacillary angiomatosis
Oropharyngeal candidiasis
Persistent, recurrent, or difficult to treat vaginal candidiasis
Cervical dysplasia or carcinoma in situ
Oral hairy leukoplakia
Idiopathic thrombocytopenic purpura
Listeriosis
Pelvic inflammatory disease (especially if complicated by tuboovarian abscess)
Peripheral neuropathy
Herpes zoster, two or more episodes involving more than one dermatome

Data from Centers for Disease Control and Prevention. 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR. *1992;41 (RR-17): 1-19.*

Table 45–3 HIV CLINICAL CATEGORY C CONDITIONS

Candidiasis of bronchi, trachea, or lungs
Coccidioidomycosis (disseminated or extrapulmonary)
Cytomegalovirus disease
Disseminated or extrapulmonary histoplasmosis
Burkitt lymphoma
Mycobacterium avium complex (disseminated or extrapulmonary)
Pneumonia, recurrent
Toxoplasmosis of brain
Esophageal candidiasis
Extrapulmonary *Cryptococcus*
HIV-related encephalopathy
Intestinal isosporiasis (>1-mo duration)
Immunoblastic lymphoma
Mycobacterium tuberculosis (any site)
Progressive multifocal leukoencephalopathy
Wasting syndrome caused by HIV
Invasive cervical cancer
Intestinal cryptosporidiosis (>1-mo duration)
Herpes simplex: chronic ulcer, bronchitis, pneumonitis, or esophagitis
Kaposi sarcoma
Primary brain lymphoma
P jiroveci pneumonia
Recurrent *Salmonella* septicemia

Data from Centers Disease Control and Prevention. 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR. *1992;41(RR-17).*

Diagnostic Evaluation

The standard screening test for HIV infection is the detection of HIV antibodies using the enzyme-linked immunosorbent assay (ELISA). **Samples that are repeatedly positive on ELISA testing must be confirmed by Western blot testing.** The Western blot test is an electrophoresis that detects antibodies to HIV antigens of specific molecular weights.

When HIV is diagnosed, a complete history and physical examination should be performed. Emphasis should be placed on identifying comorbid conditions, determining the presence of any category B or C conditions, reducing risky behaviors, and assisting with coping strategies. **HIV is reportable to local health authorities, but partner notification laws vary by state,** so it is important to know the local regulations.

Before instituting therapy, laboratory testing should include HIV genotype testing to identify strains that may be resistant to therapy. HIV RNA levels can help to assess disease activity. CD4 lymphocyte counts should be measured at baseline and, generally, every 3 to 6 months thereafter to monitor for

disease staging, progression, and the risk of complications. A complete blood count (CBC), comprehensive metabolic panel, and urinalysis should be performed at baseline and periodically thereafter to monitor for complications of HIV and of the medications that are used in treatment. Serology for toxoplasmosis and cytomegalovirus should also be obtained to identify organisms at risk for reactivation following immunosuppression.

Screening for other sexually transmitted diseases (syphilis, hepatitis B and C, gonorrhea, chlamydia) **should be performed** initially and repeated, if needed, because of any ongoing risks identified. Hepatitis B and A vaccination should be offered to those who lack immunity. A purified protein derivative (PPD) test should be done, and if initially negative, repeated annually. However, a PPD may be falsely negative if the patient is very immunosuppressed or very ill. Women should have regular Papanicolaou (Pap) smears to evaluate for cervical dysplasia or cancer.

Late Disease

HIV and the opportunistic infections it allows affect every organ system in the body. Some infections, such as tuberculosis and pneumococcal pneumonia, also affect healthy people but are greatly increased in incidence and severity in the presence of HIV. Many mildly pathologic organisms, such as *Candida*, cause unusual, severe infections in parts of the body, such as the esophagus and lungs, which they would rarely if ever affect without coinfection with HIV. Moreover some AIDS defining conditions, such as Kaposi sarcoma, can occur at a normal T-cell counts while other infections, such as cytomegalovirus retinitis and cryptococcal meningitis, are only seen in the presence of extreme immunodeficiency and very low T-cell counts. Many cancers are common in HIV-positive people, some of which, such as cervical carcinoma, are found in the non–HIV-infected population while others, such as primary CNS lymphoma, are extremely rare outside of the HIV infected. Moreover, HIV infection damages the body directly and leads to such conditions as HIV-related dementia and HIV-associated nephropathy. Without antiretroviral therapy, AIDS is a universally fatal disease.

Treatment

Because of the complexity of treatment regimens and frequently changing treatment guidelines, **patients with HIV/AIDS should be referred, in almost all cases, to a physician with expertise in treating these conditions.** In general, antiretroviral therapy is used in patients who have AIDS (by laboratory or clinical criteria), who have symptoms of disease, or who are pregnant (to reduce the risk of vertical transmission). Updated guidelines on HIV/AIDS treatment and monitoring can be obtained by going to **http://www.aidsinfo.nih.gov.**

Prophylactic treatments to reduce the risk of infection are also important in immunosuppressed patients. HIV patients should receive annual influenza

vaccination and should be offered pneumococcal vaccination (preferably before the CD4 count falls to less than 200 cells/μL). Live virus vaccines are contraindicated in both HIV patients and their close (household) contacts. Prophylaxis against *P jiroveci* pneumonia should be instituted using TMP-SMX when the CD4 count falls to less than 200 cells/μL and *Mycobacterium avium–intracellulare* complex prophylaxis, using azithromycin or clarithromycin, is recommended if the CD4 count falls to less than 75 cells/μL.

Comprehension Questions

45.1 A 42-year-old woman who is known to be HIV positive is found to have a CD4 count of 125 cells/mm^3. She is on antiretroviral therapy. She has not experienced any AIDS defining illness. She continues to use IV drugs and abuse alcohol. She does not regularly take her antiretroviral medication and is often lost to follow-up. Which of the following treatments is most appropriate at this time?

A. Initiate fluconazole for candidiasis prophylaxis.
B. Initiate antiviral treatment for *H zoster* prophylaxis.
C. Initiate TMP-SMX for *P jiroveci* pneumonia prophylaxis.
D. Initiate Clarithromycin for *Mycobacterium avium*–intracellulare complex prophylaxis.

45.2 A 25-year-old previously healthy man presents to the emergency room after experiencing a generalized tonic-clonic seizure that lasted 30 seconds. He has been experiencing headaches over the past 6 months but no other associated symptoms. His mother states that she witnessed him to have two previous seizures. The history is noted for being sexually promiscuous and using IV illicit drugs. The result of his last HIV test is unknown. On neurologic examination he is noted to have increased tone on the right and decreased right arm swing when walking. The remainder of his neurologic examination is normal. A CT scan of the head with contrast reveals that he has a ring-enhancing lesion measuring 15 mm over the left motor strip region and a 12-mm ring-enhancing lesion in the left basal ganglia. Which of the following is an AIDS-defining condition?

A. Oral thrush
B. Cervical carcinoma in situ
C. Listeriosis
D. Kaposi sarcoma

45.3 A woman comes to the office after being diagnosed with HIV when she went to donate blood. She admits to multiple recent sexual partners with whom she did not use a condom. Her T-cell count is 400 and her tests for hepatitis B and C are negative. She does not remember ever having chicken pox. She has not received the hepatitis B or varicella vaccines and has never travelled outside the country. She currently has a temperature of 99.4°F (37.4°C). Which of the following vaccines is contraindicated in this patient?

A. Hepatitis B vaccine
B. Influenza vaccine
C. Tetanus vaccine
D. Varicella vaccine

45.4 A 32-year-old housekeeper working at a clinic where a significant number of HIV infected patients are seen was stuck by an inappropriately discarded needle while cleaning up a room. The needle had no obvious blood on it and she was unsure which patient the needle was used upon. She cleaned the stick with rubbing alcohol and an antibacterial ointment. She waited 2 days before reporting the injury because she was fearful to admit her mistake. After prompting from her husband, she now desires to know what she should do. Which of the following is the best next step for this patient?

A. Recommend postexposure prophylaxis (PEP) since the exposure happened at a clinic with a risk that the needle was contaminated with HIV.
B. Do not give PEP because it has been more than 2 hours since the exposure.
C. Offer PEP after explaining risks and benefits of treatment, because this percutaneous exposure came from an unknown source at a high-risk clinic.
D. Do not give PEP because it has been definitely shown not to decrease the transmission of HIV.

ANSWERS

45.1 **C.** With this level of cell count, the patient should continue antiretroviral therapy and start *P jiroveci* pneumonia prophylaxis. The level is not yet low enough to recommend *Mycobacterium avium*–intracellulare complex prophylaxis.

45.2 **D.** Kaposi Sarcoma is an AIDS-defining condition. All of the other conditions listed are clinical category B.

45.3 **D.** The varicella vaccine is a live attenuated virus and is contraindicated in HIV.

45.4 **C.** Percutaneous unknown source exposures have an indeterminate risk. Current guidelines recommend that unknown source exposures generally do not warrant PEP. However, in high-risk settings, workers should be counseled about the risks and benefits of the medication and allowed to choose PEP should they desire.

Clinical Pearls

- Because of the complexity of the drug regimens and the ever-changing guidelines, persons with HIV should be comanaged with an infectious disease specialist or other physician with expertise in treating HIV.
- The use of antiretroviral therapy during pregnancy can reduce the risk of vertical transmission of HIV. Women with high HIV viral titers at term should be offered elective cesarean delivery, as this further reduces the risk of vertical transmission.
- The risk of transmission of HIV to health-care workers by accidental needle sticks from HIV-infected patients is very low. It is important to report these injuries promptly, as early prophylactic treatment can significantly lower the risk of developing HIV disease.

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Case 46

A 33-year-old African-American man presents to the office for an acute visit with nausea and diarrhea that he has had for the past week. Along with these symptoms, he has had a low-grade fever, some right upper quadrant (RUQ) abdominal pain, and has noticed that his eyes seem yellow. He has no significant medical history and takes no medications regularly. He denies alcohol, tobacco, or IV drug use. He works as a pastor in a local church that went on a mission to build a medical clinic in a rural area of Central America about 5 weeks ago. He had a mild case of traveler's diarrhea while there, but otherwise has felt well. On examination, he is a well-developed man who appears to be moderately ill. His temperature is 99.8°F (37.6°C), his blood pressure is 110/80 mm Hg, his pulse is 90 beats/min, and his respiratory rate is 14 breaths/min. He has a prominent yellow color to his sclera and under his tongue. His mucous membranes are moist. Lung and cardiac examinations are normal. His abdomen has normal bowel sounds and tenderness in the right upper quadrant. His liver edge is palpable just below the costal margin. There are no other masses felt, no rebound, and no guarding. On rectal examination, he has clay-colored soft stool that is fecal occult blood test negative.

- What is the most likely diagnosis?
- When and how did he most probably contract this illness?
- How can you confirm the diagnosis?
- What is the treatment at this point?

ANSWERS TO CASE 46:
Jaundice

Summary: A 33-year-old man with no significant medical history develops diarrhea, abdominal pain, and jaundice about a month after traveling to Central America. He is noted to have yellow eyes and tender hepatomegaly.

- **Most likely diagnosis:** Acute infection with hepatitis A.
- **Most probable timing and source of infection:** Ingestion of contaminated food or water while on his mission to Central America 5 weeks earlier.
- **Test to confirm the diagnosis:** Antihepatitis A immunoglobulin (Ig) M.
- **Treatment of acute hepatitis A:** Supportive care and symptomatic treatment for the patient; report infection to local health department; consider giving Ig prophylaxis to close household or sexual contacts.

ANALYSIS

Objectives

1. Develop a differential diagnosis for adults with jaundice.
2. Know the symptoms, management, complications, and modes of transmission of hepatitis A, B, and C.
3. Be able to interpret the results of hepatitis viral serology tests.

Considerations

This presentation of diarrhea along with nonspecific, crampy abdominal pain is most often caused by viral gastroenteritis. However, this patient has several symptoms and signs that serve as clues to point to other potential diagnoses. Of particular importance, the complaint of yellow eyes should prompt an evaluation for jaundice.

Bilirubin is a breakdown product of red blood cells. During the breakdown of hemoglobin, bilirubin is formed and bound to albumin, which carries it to the liver. In the liver, a portion of the bilirubin is made water soluble by conjugation to a glucuronide. This "conjugated bilirubin" is excreted in the bile and then largely excreted in the stool. Bilirubin that is not conjugated ("unconjugated bilirubin") in the liver remains bound to albumin.

Most cases of **jaundice can be characterized as having prehepatic, hepatic, or posthepatic causes.** Prehepatic jaundice is most often from hemolysis of red blood cells, which overwhelms the liver's ability to conjugate and clear the bilirubin through its normal pathways. This produces a hyperbilirubinemia that is primarily unconjugated.

Hepatic causes of jaundice can lead to either unconjugated or conjugated hyperbilirubinemia. Viruses, such as hepatitis, and alcohol reduce the liver's ability to transport bilirubin *after* it has been conjugated, resulting in a conjugated hyperbilirubinemia.

Posthepatic jaundice is usually caused by obstruction to the flow of bile through the bile ducts. This can be caused by bile duct stones, strictures, or tumors that narrow or block the ducts. Posthepatic jaundice is, therefore, a conjugated hyperbilirubinemia.

APPROACH TO Jaundice

DEFINITIONS

CAPUT MEDUSA: Dilated superficial periumbilical veins that usually result from shunting associated with severe portal hypertension

SPIDER VEINS: Dilated, small, superficial veins that appear as red, blue, or purple web-like formations, most often seen on the legs and face

CLINICAL APPROACH

History and Examination

The most important information in the diagnostic evaluation usually comes from the history. In patients presenting with jaundice, the history should be thorough and should include questions focused on identifying the common causes of jaundice. Specific information should include when the jaundice commenced and whether it is of acute or gradual onset. The presence of gastrointestinal symptoms, such as abdominal pain, nausea, vomiting, diarrhea, or changes in stool color can be significant. Itching is common in jaundice and this symptom may, in fact, precede the onset of the yellow color.

Associated symptoms, such as unintended weight loss or the development of adenopathy may lead to the consideration of certain diagnoses, including malignancies. Bruising or bleeding disorders may suggest severe hepatic dysfunction that is interfering with the production of clotting factors. Increasing abdominal girth may be caused by ascites and peripheral edema by obstruction of venous return from the lower extremities or hypoalbuminemia.

A complete review of the past medical history is necessary. **Any medications, whether prescription, nonprescription, or herbal supplements, should be reviewed.** Acetaminophen is a widely used over-the-counter agent that, in toxic amounts, can cause hepatocellular damage. Numerous herbal agents have been associated with liver damage as well.

The **social history is of critical importance in a patient with jaundice.** The abuse of alcohol is the most common cause of cirrhosis. IV drug use or unsafe sexual practices can lead to infection with hepatitis B or C. Hepatitis is also associated with getting tattoos if unsterilized equipment is used. Travel history, especially the location and timing of any international travel, can lead to the consideration of hepatitis A.

A comprehensive physical examination is also important in the workup of someone with jaundice. Along with a general physical examination, certain areas should be emphasized. Jaundice may first be noticed as a yellowing of the sclera, especially in persons with darker skin types. Yellow discoloration can also commonly be seen under the tongue.

Examination of the skin should document the jaundice and also look for clues to its cause. The stigmata of alcohol abuse (eg, caput medusa, spider veins) or IV drug use (needle track marks) should be noted. Large hematomas, by themselves, could be a cause of jaundice as the blood resorbs. Signs of bruising or bleeding should also be documented.

Abdominal examination must include, among other things, evaluation of the general contour of the abdomen, the presence of any ascites, the presence of organomegaly, and any tenderness. Hepatomegaly may or may not occur as a part of liver disease. Right upper quadrant tenderness can be associated with acute hepatitis but also with gallstone disease. Splenomegaly could suggest portal hypertension from cirrhosis, could be caused by malignancy, or by splenic sequestration of damaged RBCs.

Laboratory Testing

The most important initial laboratory evaluation of jaundice is the bilirubin level, which is usually reported as both a total bilirubin and direct bilirubin. **The reported direct bilirubin is a measurement of the conjugated bilirubin level.** Unconjugated bilirubin can be determined by subtracting the directed bilirubin from the total bilirubin.

The relative relationship of conjugated and unconjugated bilirubin in a jaundiced person can be indirectly evaluated by performing a urinalysis. **Conjugated bilirubin is excreted in the urine, whereas unconjugated bilirubin is not.** A urinalysis on a jaundice patient who has a high level of bilirubin suggests that the patient has a conjugated hyperbilirubinemia; absence of bilirubin on the urinalysis suggests that it is an unconjugated hyperbilirubinemia.

UNCONJUGATED HYPERBILIRUBINEMIA

A mild unconjugated hyperbilirubinemia, usually identified as an incidental finding when liver enzymes are tested for some other reason, is often caused by **Gilbert syndrome.** Gilbert syndrome is a congenital reduction of conjugation of bilirubin in the liver. It occurs in approximately 5% of the population and is of no health significance. Occasionally, the bilirubin level will increase

during times of illness and then recover to its baseline, slightly elevated level, after the illness resolves. In a patient with mildly elevated unconjugated bilirubinemia, otherwise normal liver enzymes and complete blood count (CBC), and who is otherwise well, no further workup is indicated.

Hemolysis can cause an unconjugated hyperbilirubinemia in proportion to the amount of hemolysis that occurs. It is most often diagnosed by identification of anemia along with the presence of red cell fragments or abnormalities (spherocytosis, thalassemias, sickle cell disease, malaria, thrombotic thrombocytopenic purpura [TTP], and hemolytic uremic syndrome [HUS]). The management is to treat the cause of the hemolysis.

CONJUGATED HYPERBILIRUBINEMIA

Hepatitis A is a viral infection of the liver primarily transmitted via fecal-oral contamination and accounts for 30% of acute viral hepatitis in the United States. Contaminated food and water are the primary sources of infection, although risks also include drug use (both injection and noninjection), male-male sexual contact, and working in a daycare setting. Hepatitis A infection is widespread in Africa, Asia, and Central and South America. Travelers to these areas are at risk for infection.

Hepatitis A causes a self-limited illness characterized by jaundice, fever, malaise, and abdominal discomfort. The incubation period is 2 to 8 weeks and transmission is possible for 2 to 3 weeks after symptoms begin. While the symptoms can be mild, even asymptomatic in younger patients, there is an approximately 2% fatality rate in those older than age 50 years. The illness tends to last for 4 to 6 weeks, although some people have an illness that will last up to 6 months. There is no specific treatment for hepatitis A. Supportive care and symptomatic treatments are indicated.

Hepatitis A is diagnosed based on the presence of a conjugated hyperbilirubinemia, elevated hepatic transaminases, and serology. An acute infection causes an elevation of antihepatitis A virus (HAV) IgM. An elevated anti-HAV IgG but negative IgM indicates a history of a previous hepatitis A infection but not acute illness.

Hepatitis A vaccination is available and recommended for those at high risk, including travelers to endemic areas, persons with chronic liver disease, men who have sex with men, or children who live in areas with high rates of the illness. Household or sexual contacts of persons infected with hepatitis A can be offered prophylaxis with injections of immunoglobulin.

Hepatitis B has infected 2 billion people worldwide and there are 350 million chronic carriers. It is a viral infection transmitted via contact with contaminated blood or body fluids. Sexual contact and needle sharing are common mechanisms of infection. Hepatitis B may also be vertically transmitted from mother to baby. The incubation period from exposure to clinical symptoms is 6 weeks to 6 months. Only 50% of infections with hepatitis B are symptomatic. Approximately 1% of infections result in hepatic failure and death.

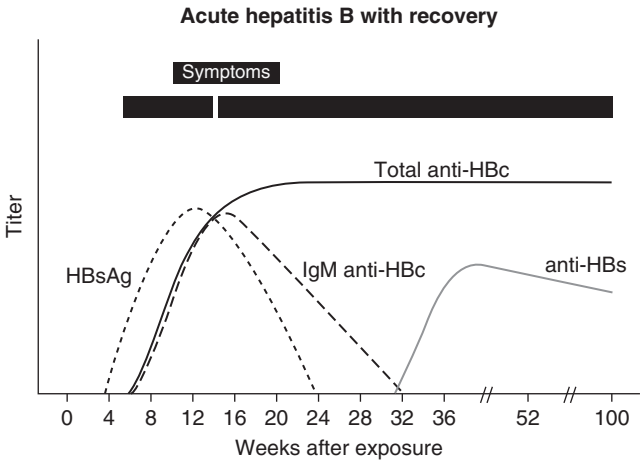

Figure 46–1. Acute hepatitis B with recovery. (*Reproduced with permission from Briscoe DB.* Lange Q&A: USMLE Step 3. *4th ed. New York, NY: McGraw-Hill; 2005:48.*)

Along with the acute symptoms, which are similar to hepatitis A, hepatitis B can cause a chronic infection. **Chronic hepatitis B is highly related to the age of the patient**—90% of infected infants, 60% of children younger than age 5 years, and 10% to 15% infected adults develop chronic hepatitis B, which can lead to cirrhosis and hepatocellular carcinoma. **Hepatitis B causes up to 80% hepatocellular carcinoma worldwide**.

Serologic studies, using several markers, are necessary to determine the presence and type of hepatitis B infection that is present. Hepatitis B surface antigen (HBsAg) is present in both acute and chronic infections. Its presence is associated with contagiousness to others. Patients with the e antigen (HBeAg) are 100 times more infectious than those lacking the HBeAg. **Antibody to the surface antigen (anti-HBs) is seen in resolved infections and is the serologic marker produced after hepatitis B vaccination.** An IgM antibody to the hepatitis B core antigen (anti-HBcAg IgM) is diagnostic of an acute infection. A measurable level of HBsAg with a negative anti-HBcAg IgM is diagnostic of chronic hepatitis B. Figures 46–1 and 46–2 show the serologic studies associated with acute hepatitis B infection and chronic hepatitis B infection, respectively.

Acute hepatitis B infection is treated supportively. Persons with chronic hepatitis B may be candidates for antiviral therapy. They should be referred to a specialist both to evaluate the appropriateness of therapy and to monitor for the development of hepatocellular carcinoma or cirrhosis.

Hepatitis B vaccination is universally recommended for children. Vaccination is also recommended for adults at high risk of disease, including health-care and public safety workers, IV drug users, persons with chronic liver disease, and dialysis patients.

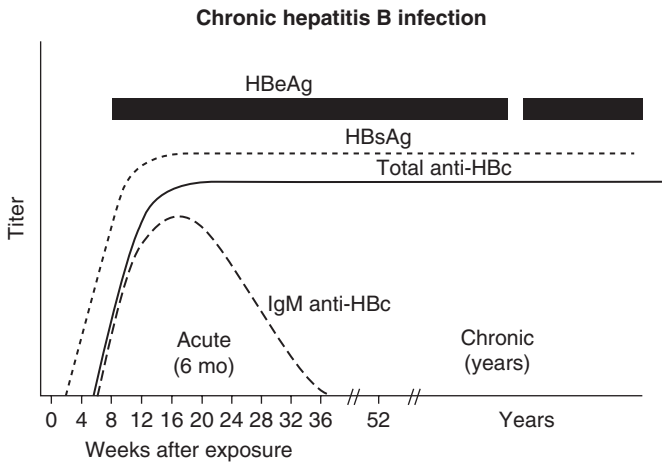

Figure 46–2. Chronic hepatitis B infection. *Reproduced with permission from Briscoe DB.* Lange Q&A: USMLE Step 3. *4th ed. New York, NY: McGraw-Hill; 2005:48.*

Hepatitis C, formerly known as non-A, non-B hepatitis, is the most common cause of chronic liver disease in the United States, with more than 4 million infected persons. Transmission occurs via exposure to infected blood or body fluids via sexual contact, needle sharing, or accidental exposure of health-care workers, and by vertical transmission. Blood or blood-product transfusion was a common source of exposure prior to 1992.

The virus can be detected in the blood within 1 to 3 weeks of exposure, with liver cell injury detectable in 4 to 12 weeks. Most infections are asymptomatic, but hepatitis C can cause an acute illness with jaundice, malaise, and anorexia. **Of those infected with hepatitis C, 60% to 85% will develop a chronic infection,** with measurable levels of hepatitis C virus RNA (HCV RNA) for more than 6 months.

Chronic hepatitis C can lead to cirrhosis and hepatocellular carcinoma. Disease activity can be monitored by serial measurements of HCV RNA along with transaminases levels. Chronic hepatitis C can be treated with antiviral therapy, using ribavirin and/or interferon, but results are variable and there is no cure. Sometimes liver transplant is used as a last resort. There is currently no vaccination available for hepatitis C.

Hepatitis D is a rare cause of viral hepatitis that uses the viral envelop of Hepatitis B to infect its host and thus requires coinfection of Hepatitis B and D. It is endemic in the Mediterreanean, Middle East, and South America. In coinfection 10% or less will become chronically infected. Interferon helps to treat it and it can be prevented with a Hep B vaccine.

Hepatitis E is a fecal-orally transmitted viral hepatitis. It is rare in the United States. but has a very high mortality rate in the second and third trimesters for pregnant woman. Treatment is supportive and there is no immunization.

Alcohol abuse can cause an acute, severe hepatitis, or chronic fatty liver, hepatitis, and cirrhosis. Alcohol leads to a conjugated hyperbilirubinemia by impairing bile acid secretion and uptake. **Transaminase levels from alcohol abuse typically show the aspartate aminotransferase (AST) being elevated out of proportion to the alanine aminotransferase (ALT);** viral hepatitis usually causes greater elevations of the ALT (see Case 41 for a more thorough discussion of alcohol abuse).

Physical obstructions of bile drainage can also cause conjugated hyperbilirubinemia. Common etiologies include gallstones that become impacted in the bile ducts, postoperative biliary strictures, or extrinsic compression of the bile ducts by tumors, such as pancreatic cancer. Imaging of the bile system with ultrasound, computed tomography (CT) scan, or magnetic resonance imaging (MRI or magnetic resonance cholangiopancreatography) is usually diagnostic. Endoscopic retrograde cholangiopancreatography (ERCP) can be diagnostic and, in some cases, therapeutic.

Comprehension Questions

46.1 A 32-year-old man with asthma and hypertension comes in for evaluation of an elevated bilirubin level that was detected on blood work required for a preemployment physical. The bilirubin level was 2.5 mg/dL (normal up to 1.0 mg/dL) with an elevated unconjugated component. He feels well and generally drinks one beer per night. He is monogamous with his wife and has no history of IV drug abuse or tattoos. His eyes are not icteric and there are no signs of jaundice. His liver enzymes, chemistries, and complete blood count (CBC) are normal. Which of the following is the next step in his evaluation?

A. Reassurance
B. Counsel on alcohol reduction
C. Abdominal ultrasound
D. Hepatitis serologies

46.2 A 45-year-old woman was diagnosed 6 months ago with acute hepatitis B. She is unaware of how she contracted the virus. She takes no medications and since the diagnosis has started taking a multivitamin and begun to exercise. She now has the following serologies: HBsAg negative; anti-HBsAg positive; HBeAg negative; anti-HBcAg positive. Which of the following is your interpretation of these results?

A. Chronic active hepatitis B
B. Resolved acute infection
C. Resolved acute infection but contagious to sexual contacts
D. Resolved infection but at risk for reinfection in the future

46.3 A 67-year-old retired sailor comes to the doctor after 15 lb unintentional weight gain over the past 4 months. He previously had no significant medical history and feels fine except for fatigue. On examination he is slightly jaundiced, with no hepatomegaly or RUQ tenderness to palpation. He does have some mild shifting dullness in his abdomen, and significant peripheral edema. His skin is noted to have several faded tattoos. The patient most probably has which of the following serologies?

A. Positive IgG anti-HAV
B. HCV RNA present
C. Anti-HBs antibody only
D. HCV RNA present and Anti-HCV antibody

ANSWERS

46.1 **A.** This is a classic case of Gilbert disease, a benign mild elevation of unconjugated bilirubin. In the face of otherwise normal history, examination, and liver enzymes, no further workup is indicated. People with Gilbert syndrome can have icteric sclera and jaundice that worsens with stress or illness.

46.2 **B.** These serologies are consistent with resolved hepatitis B infection and ongoing immunity; the anti-hepatitis B surface antigen antibodies indicates immunity. This patient has both negative surface and e antigens, so is not at risk to spread the disease to others.

46.3 **D.** The patient probably has chronic hepatitis C that has progressed to cirrhosis causing the edema, weight gain, and ascites. Both HCV RNA and Anti-HCV antibodies are present in chronic Hep C. Hep A does not proceed to cirrhosis and Anti-HBs is present in people immunized to Hep B.

Clinical Pearls

- The acute onset of painless jaundice in a patient older than age 50 years should prompt an examination for pancreatic cancer (malignancy in the head of the pancreas causing compression of the bile ducts).
- All pregnant women should be screened for the presence of HBsAg. If positive, treating the newborns with hepatitis B immunoglobulin (HBIg) and vaccination can reduce the risk of vertical transmission.
- One of the greatest risks for the development of cirrhosis in those with chronic hepatitis C is alcohol use. Anyone with chronic hepatitis C should be counseled to avoid all alcohol intake.

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Case 47

A 52-year-old man presents to the office with approximately 2 weeks of upper abdominal pain. His symptoms are difficult for him to describe, but include some "discomfort" in the epigastric region that comes and goes. He has had some "heartburn" and nausea, but no vomiting or diarrhea. He has noticed that his stool looks darker than it used to, but he has not seen any blood. He feels full quickly after eating. He tried taking some over-the-counter antacid, which helps a little bit. His only other medication is an over-the-counter nonsteroidal anti-inflammatory drug (NSAID) that he takes "once or twice" a day because of arthritis in his knees. He does not smoke cigarettes or drink alcohol. On examination, he is pale appearing, but in no acute discomfort. He is afebrile, his blood pressure is 120/80 mm Hg, his pulse is 95 beats/min, and his respiratory rate is 14 breaths/min. Head, ears, eyes, nose, and throat (HEENT) examination is notable only for pale conjunctiva. Cardiac and pulmonary examinations are normal. His abdomen has normoactive bowel sounds and tenderness in the epigastrium. There is no mass, rebound, or guarding. Rectal examination reveals normal tone, no masses, and dark black stool that is strongly fecal occult blood test (FOBT) positive. The remainder of his examination is unremarkable.

- What is the most likely diagnosis?
- What evaluation and treatment is indicated at this point?
- What can be done to reduce the risk of recurrence of this problem?

ANSWERS TO CASE 47:
Dyspepsia and Peptic Ulcer Disease

Summary: A 52-year-old man presents with vague upper abdominal discomfort, nausea, and early satiety. He is a daily NSAID user. He appears pale on examination, suggesting that he may be anemic. He has mild abdominal tenderness and melanotic stool on examination.

- **Most likely diagnosis:** Bleeding peptic ulcer.
- **Evaluation and treatment at this point:** A stat complete blood count (CBC), discontinuation of his NSAID, upper GI endoscopy, and testing for *Helicobacter pylori*. He should be treated with a proton pump inhibitor (PPI) and antibiotics for *H pylori*, if tests confirm its presence. He may need a blood transfusion (dependent on the result of his CBC). He will also require evaluation with a colonoscopy.
- **Reduce risk of recurrence by:** Discontinuation and avoidance of NSAID or, if unable to completely discontinue, use of PPI or misoprostol with the NSAID; eradication of *H pylori*.

ANALYSIS

Objectives

1. Learn management of dyspepsia.
2. Learn the risk factors for the development of peptic ulcer disease (PUD).
3. Know how to diagnose and treat peptic ulcers.
4. Understand the role of *H pylori* in PUD, including methods for testing for and treatment of PUD.
5. Know the "alarm symptoms" for which endoscopy is indicated.

Considerations

Dyspepsia is defined as chronic or recurrent upper abdominal pain or discomfort. Approximately 10% of dyspepsia is caused by peptic ulcer disease. Other common causes include gastroesophageal reflux disease (GERD) and functional dyspepsia. The diagnostic workup and treatment of patients with dyspepsia varies and is dependent on the age of the patient, the presenting symptoms and signs, and the response to the initial management offered.

Peptic ulcer disease is a problem of the gastrointestinal tract characterized by mucosal damage secondary to pepsin and gastric acid secretion. It usually occurs in the stomach and proximal duodenum; less commonly, it occurs in the lower esophagus, the distal duodenum, or the jejunum, as in unopposed

Table 47–1 "ALARM" SYMPTOMS FOR WHICH EARLY UPPER GI ENDOSCOPY IS RECOMMENDED

Weight loss
Progressive dysphagia
Recurrent vomiting
Gastrointestinal bleeding
Family history of cancer

hypersecretory states such as Zollinger-Ellison syndrome, in hiatal hernias (Cameron ulcers), or in ectopic gastric mucosa (eg, in Meckel diverticulum).

Early diagnostic **endoscopy should be considered for patients with new-onset dyspepsia who are older than age 55 years or who have symptoms that may be associated with upper GI malignancy** (Table 47–1). For those younger than age 55 years and without alarm symptoms, testing for *H pylori*, either by urea breath test or stool antigen testing, is recommended. For those who test positive, treating the *H pylori* followed by acid-suppression therapy is indicated. For persons who test negative, empiric therapy with a PPI for 4 to 8 weeks is a cost-effective intervention. Endoscopy or reconsideration of the diagnosis should be considered for those who continue to be symptomatic following these interventions.

APPROACH TO
Dyspepsia and Peptic Ulcer Disease

DEFINITIONS

H_2 BLOCKER: Class of medications that are competitive antagonists of histamine binding to gastric parietal cell H_2 receptors, which prevents activation of the pathway that mediates release of acid into the gastric lumen.

PROTON PUMP INHIBITOR (PPI): Class of medications that suppresses gastric acid production by irreversibly inhibiting the H^+ K^+ ATPase proton pump in gastric parietal cells.

CLINICAL APPROACH

PUD is a term generally used to describe both duodenal and gastric ulcers. **Duodenal ulcers are more prevalent overall, whereas gastric ulcers are more common in NSAID users.** Risk factors for the development of PUD include *H pylori* infection, the use of an NSAID, cigarette smoking, and personal or family history of PUD. Black and Hispanic populations have a higher

Table 47–2 CAUSES OF PEPTIC ULCERS

CAUSES	ETIOLOGY	COMMENTS
Common causes	Helicobacter pylori infection	Gram-negative, motile spiral rod found in 48% of patients with peptic ulcer disease
	NSAIDs	5% to 20% of patients who use NSAIDs over long periods develop peptic ulcer disease NSAID-induced ulcers and complications are more common in the elderly, those with concomitant *H pylori* infection, or those on steroid or anticoagulant
Other/rare causes	Other medications	Steroids, bisphosphonates, potassium chloride, chemotherapeutic agents (eg, intravenous fluorouracil)
	Acid-hypersecretory states (eg, Zollinger-Ellison syndrome)	Multiple gastroduodenal, jejunal, or esophageal ulcers
	Malignancy	Gastric cancer, lymphomas, lung cancers
	Stress	After acute illness, multiorgan failure, ventilator support, extensive burns (Curling ulcer), or head injury (Cushing ulcer)

Adapted from *Kurata JH, Nogawa AN. Meta-analysis of risk factors for peptic ulcer. Nonsteroidal anti-inflammatory drugs, Helicobacter pylori, and smoking.* J Clin Gastroenterol. 1997;24:2-17.

likelihood of developing PUD as well. The lifetime risk of developing PUD in the United States is approximately 10%. **Table 47–2** summarizes other causes of PUD.

History and Examination

Dyspepsia symptoms are common and there is significant overlap between the symptoms of PUD, GERD, and functional dyspepsia. Patients with symptoms primarily of heartburn or acid regurgitation are more likely to have GERD. **Classic symptoms associated with PUD include epigastric abdominal pain that is improved with the ingestion of food, or pain that develops a few**

hours after eating. Nocturnal symptoms are also common with PUD. The symptoms are often gradual in onset and present for weeks or months. Patients often self-medicate with over-the-counter antacid medications, which usually provide some relief, prior to presenting to the physician.

The examination should both attempt to confirm your suspicion of PUD and rule out other diagnoses that may present with abdominal pain. PUD often will only have the examination finding of epigastric tenderness. The presence of GI bleeding may be documented by stool occult blood testing; however, the bleeding from PUD may be episodic and a negative single office occult blood test does not completely rule out bleeding. Signs of anemia (pale conjunctiva or skin, tachycardia, hypotension, orthostasis) should be evaluated and managed as needed.

Many potential diagnoses must be considered in your differential. Finding right upper quadrant tenderness may suggest gallbladder or biliary disease. Appendicitis, while classically causing right lower quadrant pain, may present with only vague abdominal symptoms (especially with a retrocecal appendix). Epigastric pain radiating to the back and associated with nausea and vomiting may be pancreatitis. Pelvic infections, pelvic pathology, and even ectopic pregnancy must be considered as possibilities in women. Myocardial ischemia should be considered in those at risk.

Helicobacter pylori

H pylori is a corkscrew-shaped gram-negative bacillus that is the causative agent of most non–NSAID-related ulcers. *H pylori* is also associated with the development of gastric cancer. The **presence of the organism is associated with a 5 to 7 times increased risk of the development of PUD.** How *H pylori* is transmitted is not entirely understood.

Several tests are available to diagnose infections with *H pylori*. **Stool antigen testing is now the preferred non-invasive office test for H pylori,** due to its superior positive predictive value and ability to be used posttreatment to test for eradication. However, for this test to be accurate, patients must not have been treated with PPIs for at least 2 weeks prior to testing. **Serologic testing for anti–*H pylori* antibodies** is widely available, inexpensive, and noninvasive. It is highly sensitive for the presence of a history of infection but **cannot distinguish an active infection from a treated infection.**

Active infection can be confirmed by **urea breath testing.** This test is performed by having the patient ingest a carbon-labeled urea compound, which is then metabolized by urease from the *H pylori* organism. The labeled CO_2 released by this process is measured in exhaled breath. This test is highly sensitive and specific, but is limited by availability and expense.

The **gold standard** for diagnosis is **endoscopy with biopsy testing for** *H pylori*. The bacterium can either be visualized microscopically using a variety of staining methods, cultured, or detected by rapid testing of the specimen. Endoscopy also allows for direct visualization of ulcers and evaluation for the

presence of malignancy or other pathology in the esophagus, stomach, or duodenum. Endoscopy is invasive and expensive, limiting its utility to certain clinical situations.

Complications of PUD

About 25% of patients with peptic ulcer disease have a serious complication such as hemorrhage, perforation, or gastric outlet obstruction. Silent ulcers and complications are more common in older patients and in patients taking NSAIDs.

Upper gastrointestinal bleeding occurs in 15% to 20% of patients with peptic ulcer disease. It is the most common cause of death and most common indication for surgery in the disease. The risk of rebleeding and death is increased based on age, comorbidities, and hemodynamic status.

Management of Suspected PUD

After the initial history and physical examination, focused testing appropriate to evaluate the suspected clinical syndromes should be ordered. A CBC should be drawn to evaluate for anemia, even when stool studies are negative for occult blood. A patient who has been vomiting or not eating should have basic chemistry studies performed. Liver enzymes, amylase, and lipase tests may be ordered when biliary or pancreatic disease is suspected. An ECG can be done if cardiac disease is a consideration, and an upright chest x-ray is the test of choice for possible abdominal organ perforation. Abdominal ultrasonography is indicated when gallstones are suspected. A pregnancy test should be ordered on reproductive-age women, and cervical cultures performed if infection is suspected.

Patients with significant anemia, hemodynamic instability (hypotension, tachycardia, orthostasis), or suspected acute abdomen should be hospitalized. IV rehydration and blood transfusion should be performed when necessary. Urgent surgical evaluation should be obtained if an acute abdomen is present.

Dyspepsia in patients younger than age 55 years with no alarm symptoms can be managed with a noninvasive *H pylori* "test-and-treat" protocol. A **test for an active *H pylori* infection (stool antigen or serum IgA ELISA [enzyme-linked immunosorbent assay] antibodies) should be performed.** A negative test rules out ulcer in dyspeptic patients. If positive, treatment to eradicate the infection, along with a PPI to suppress acid production, should be prescribed (Table 47–3 lists *H pylori* treatment regimens).

Generally PPI have greater efficacy in suppressing acid production and hastening ulcer healing than H2 blockers. Those with no evidence of active infection can be treated with acid suppression alone for 4–6 weeks. If symptoms resolve, no further testing is indicated. Along with treatment, offending agents, such as NSAIDs and tobacco, should be discontinued.

Table 47–3 HELICOBACTER PYLORI TREATMENT REGIMENS

DRUG	DOSE
Triple Therapy	
Bismuth subsalicylate *plus* Metronidazole *plus* Tetracycline	2 tabs qid 250 mg qid 500 mg qid
Ranitidine bismuth citrate *plus* Tetracycline *plus* Clarithromycin or metronidazole	400 mg bid 500 mg bid 500 mg bid
Omeprazole (lansoprazole) *plus* Clarithromycin *plus* Metronidazole or Amoxicillin	20 mg bid (30 mg bid) 250 or 500 mg bid 500 mg bid 1 g bid
Quadruple Therapy	
Omeprazole (lansoprazole) Bismuth subsalicylate Metronidazole Tetracycline	20 mg (30 mg) daily 2 tabs qid 250 mg qid 500 mg qid

Data from Del Valle J. Peptic ulcer disease and related disorders. In: Fauci AS, Braunwald E, Kasper DL, et al, eds. Harrison's Principles of Internal Medicine. *17th ed. New York, NY: McGraw Hill Medical; 2008:1863.*

Patients older than age 55 years or with alarm symptoms should be referred for upper GI endoscopy to exclude the possibility of malignancy. Endoscopy is preferred over radiologic procedures because of better visualization and because of the ability to perform biopsy. Endoscopy also can be therapeutic, if a source of bleeding can be identified and cauterized. **A patient who is older than age 50 years and who has blood in the stool should also undergo a colonoscopy regardless of the upper endoscopic findings,** to ensure that there is not a colon cancer also contributing to the GI blood loss.

Surgical treatment for PUD is rarely needed. However it may be warranted for cases of hemorrhage that cannot be controlled, perforation, or obstruction.

Comprehension Questions

47.1 A 30-year-old woman with no known medical problems comes to you for advice. She attended a health fair where she tested positive for *H pylori* on a blood test. She has had no abdominal discomfort, nausea, vomiting, or diarrhea. Her stool has been negative for blood. She occasionally has to use over-the-counter antacids after eating spicy foods. Which of the following would you tell her about the result of this test?

A. She may or may not have an *H pylori* infection.
B. She probably has a peptic ulcer.
C. She has an *H pylori* infection but may or may not have an ulcer.
D. She should be treated immediately for *H pylori*.

47.2 A 62-year-old man presents to clinic with increasing shortness of breath and fatigue. Cardiac examination is negative and lungs are clear to auscultation bilaterally. No jaundice, JVD, or peripheral edema is noted. Mucous membranes are pink with no evidence of cyanosis and capillary refill is good. CBC reveals a microcytic anemia and a gastric ulcer is diagnosed on upper GI endoscopy. A biopsy and testing confirm an *H pylori* infection. His last colonoscopy was 2 years ago and was normal. Which of the following further testing is indicated at this time?

A. Upper GI radiographic series with small bowel follow through
B. Abdominal ultrasound
C. Colonoscopy
D. Urea breath test

47.3 A 41-year-old man presents for evaluation of upper GI discomfort that he has had for about 2 months. He says that he has a "full" sensation in the epigastric region. He recently began smoking after increased stress at work. He has had no blood in his stool, no vomiting, and no dysphagia. He has lost about 10 lb but does not exercise. His mother has hemorrhoids but no family member has ever had colon cancer. He has never had a colonoscopy. Which of the following is most appropriate?

A. *H pylori* "test and treat"
B. Empiric therapy for *H pylori*
C. FOBT with reassurance if negative
D. Referral for endoscopy

47.4 A 19-year-old woman arrives at the emergency room with a 15-hour history of abdominal pain, nausea, and vomiting. She was awoken early in morning by severe abdominal pain. She does admit to drinking heavily the prior evening that is not unusual during the weekends. She does not use NSAIDs regularly. Her blood pressure is 100/60 mm Hg and her pulse rate is 130 beats/min, respirations are 14 breaths/min, her temperature is 39°C. Acute abdominal series upon admission displayed substantial amount of free air under the right hemidiaphragm. Which of the following is the most likely diagnosis?

A. Perforated peptic ulcer
B. Alcohol-related gastritis
C. Appendicitis
D. Gastroenteritis
E. Kidney stones

ANSWERS

47.1 **A.** *H pylori* blood tests are testing for anti–*H pylori* antibodies. They cannot distinguish active infections from old infections nor can they diagnose the presence of ulcers. Treating a positive serum test in an asymptomatic person is not indicated.

47.2 **C.** The presence of blood in the stool or anemia in a patient older than age 50 years, even when an ulcer is found, is an indication for colonoscopy, as this may also represent a presentation of a concomitant colon cancer. An urea breath test may be beneficial after completion of treatment to confirm eradication of the infection.

47.3 **D.** This patient presents with the alarm symptom of weight loss. He should be referred for early endoscopy.

47.4 **A.** The acute abdomen and free air under the diaphram indicates a perforated viscus. This patient has perforated ulcer with hemodynamic instability. Additional workup includes a chemistry panel, CBC, and urgent laparotomy.

Clinical Pearls

- Persons who require long-term NSAID therapy may benefit from testing for active *H pylori* infection, followed by eradication, if positive, as this may lower their risk of developing an ulcer. PPI therapy, along with the NSAID, can also lower the risk.
- Commonly held beliefs, such as ulcers being caused by stress or spicy foods, are incorrect. The vast majority of ulcers are caused by *H pylori* and NSAIDs.

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Case 48

An 18-month-old girl is brought to the office by her mother for an acute visit because of a rash. She had a subjective high fever for the past 3 days, along with some mild respiratory symptoms. She was given acetaminophen for the fever but no other medications. The fever has gone down in the past day, but today she developed a rash. The rash came up suddenly, starting on the trunk and spreading to the extremities. The child has no significant medical history and no known sick contacts, although she attends day care 3 days a week. On examination, she is mildly fussy but easily consolable in her mother's lap. She has a noticeable erythematous rash of small macules and papules that blanch on palpation. The remainder of her examination is normal.

- What is the most likely diagnosis?
- What is the most likely cause of this illness?
- What is the appropriate treatment?

ANSWERS TO CASE 48:
Fever and Rash

Summary: An 18-month-old girl is brought in for evaluation of a rapidly spreading rash that started after 3 days of fever. She has diffuse, blanching, erythematous macules, and papules but otherwise appears well.

- **Most likely diagnosis:** Roseola
- **Most likely cause of the illness:** Human herpes virus 6 (HHV-6)
- **Treatment:** Supportive only, as the rash is likely to resolve in 24 to 48 hours

ANALYSIS

Objectives

1. Be able to identify common rashes associated with viral infections in children.
2. Know the appropriate management of febrile illness associated with rashes in children.

Considerations

This toddler has a history of fever, and rash that is diffuse, erythematous papules. This is most likely due to roseola, caused by human herpes virus 6 (HHV-6). HHV-6 is a ubiquitous virus that infects most children before the age of 3 years, although most infections are asymptomatic. The virus has an incubation period of 1 to 2 weeks and causes a prodromal illness associated with mild respiratory symptoms and a high fever.

APPROACH TO
Fever and Rash

DEFINITIONS

ENANTHEM: An eruption on a mucous membrane as a symptom of a disease.

EXANTHEM: An eruption on the skin as a symptom of a disease.

CLINICAL APPROACH

Febrile illness and rashes are extremely common presentations in family medicine and pediatric offices. Most of the time these presentations represent mild, self-limited illnesses that require no specific therapy. However, some of these presentations will represent serious infections that need urgent intervention. Rashes associated with fever may be caused by viruses, bacteria, spirochetes, drug reaction, or autoimmune diseases. The patient history should attempt to identify any exposures that may cause these syndromes. Specific information that may be helpful include the duration of the illness, other associated symptoms, contact with any other ill person, history of recent travel, use of medications, or exposure to animals and insects (eg, ticks). A review of immunization status is critical, as many vaccine preventable diseases can cause fever and rash. **Immunization does not guarantee immunity** but may result in a less-severe presentation of the disease.

A thorough physical examination with a complete skin examination should be performed. Examination findings can both lead to a specific diagnosis and identify complications of the causative agent. For example, the presence of exudative pharyngitis along with fever and rash may suggest scarlet fever caused by a group A *Streptococcus* infection while an abnormal lung examination in a patient with crops of vesicles of different ages may lead to a diagnosis of varicella (chicken pox) complicated by pneumonitis.

The ability to accurately describe skin lesions is necessary for documentation purposes. It is also important when you are not certain what the diagnosis is. Knowing the definitions of macules, papules, pustules, and the like will make it much easier and more accurate when you look for information in a textbook or journal or discuss a case with a colleague or consultant. The better the information that you can provide, the more likely you are to get correct information in return. See Case 13 for definitions of many of the terms used to describe common skin lesions.

COMMON VIRAL INFECTIONS

Roseola

Human herpes virus 6 is a ubiquitous virus that infects most children before the age of 3 years, although most infections are asymptomatic. The virus has an incubation period of 1 to 2 weeks and causes a prodromal illness associated with mild respiratory symptoms and a high fever that can range from 101 to 106°F (37.9-41.1°C).This prodromal illness tends not to last for longer than 5 days. **Following defervescence, a characteristic rash appears suddenly.** It is an erythematous maculopapular eruption that starts on the trunk and spreads rapidly to the extremities, with sparing of the face. The rash tends to disappear in 1 to 2 days. The diagnosis is primarily clinical, based on the history and

examination. Because of the short-lived nature of the disease, no treatment is usually required other than reassurance.

Varicella

The varicella zoster virus is a highly contagious virus that causes two clinical syndromes. **Chicken pox** is the more common childhood infection. A typical case of chicken pox includes a fever and a rash, which tends to develop in clusters. The initial exanthem is often **papules or vesicles on an erythematous base,** described as "dewdrops on a rose petal." The vesicles then progress to shallow, crusted erosions. Patients may also develop enanthems, with lesions on the oral, nasal, or gastrointestinal mucosa. In rare cases, serious complications may develop, which include encephalitis, meningitis, and pneumonitis. Super-infection of the vesicles with bacteria, most commonly group A *Streptococcus* and *Staphylococcus aureus*, is a particularly common and potentially dangerous complication. The diagnosis of varicella is usually clinical, but may be confirmed with Tzanck smear or identification of the virus by DNA PCR (polymerase chain reaction). Antiviral therapy using acyclovir, valacyclovir, or famciclovir may shorten the course of the illness in patients older than 2 years of age if started within 24 hours of onset of the exanthem. Varicella vaccination is now universally recommended at age 12 to 18 months with a booster dose at age 4 to 6 years. While the vaccine has significantly reduced the incidence of childhood chicken pox, breakthrough infections can occur in vaccinated individuals. However, these infections are usually much less severe, with fewer vesicles and little to no fever. The varicella vaccine is a live, attenuated virus and should not be given to immunocompromised or pregnant patients.

Shingles, or herpes zoster, is a reactivation of the varicella virus, which can remain dormant in a dorsal root ganglion following the initial infection. The reactivated virus causes a vesicular eruption, usually along a single dermatome that does not cross the midline. The reaction can occur at any age, but is more common in the elderly or immunosuppressed. The rash can be extremely painful and can result in a painful, postherpetic neuralgia that lasts long after resolution of the rash. Antiviral therapy started within 72 hours of the rash may reduce the incidence of the postherpetic neuralgia. A herpes zoster vaccine is now recommended for people over 60.

Erythema Infectiosum

Parvovirus B19 causes a characteristic syndrome known as erythema infectiosum or **fifth disease.** This virus tends to infect children younger than 10 years of age and occurs most commonly in the winter or spring. The child usually has a prodrome of mild fever and upper respiratory symptoms before outbreak of the rash. The rash usually starts as confluent erythematous macules on the

face, which usually spares the nose and periorbital regions. This gives the classic **"slapped cheek" appearance** that is commonly diagnostic of the infection. The facial rash lasts for 2 to 4 days, followed by a lacy, pruritic exanthem on the trunk and extremities that usually lasts for 1 to 2 weeks, but can have a relapsing course for several months. Parvovirus B19 in adults and older adolescents tends to cause a more severe illness, with rheumatic complaints such as arthritis. In patients with sickle cell disease, parvovirus B19 infection can lead to an aplastic crisis with anemia and leukopenia. The virus can also be transmitted from mother to fetus during pregnancy, resulting in fetal hydrops and pregnancy loss.

COMMON BACTERIAL INFECTIONS

Group A β-Hemolytic *Streptococcus*

Group A β-hemolytic *Streptococcus* (GAS) is associated with numerous diseases, particularly in children. It is the causative agent of streptococcal pharyngitis and its complications, which include rheumatic fever and glomerulonephritis. It can also cause impetigo and cellulitis of the skin.

The rash of **scarlet fever** usually starts about 2 days after the onset of sore throat. The rash consists of punctate, raised, erythematous eruptions that can become confluent and feel like sandpaper. The rash tends to start on the upper trunk and spreads to the rest of the trunk and the extremities. The exanthem can also be associated with an enanthem, causing the appearance of a "strawberry tongue." The rash fades and desquamation occurs 4 to 5 days after the first appearance of the rash.

GAS infections can be confirmed by rapid antigen testing or culture from a throat swab. The first-line treatment for GAS infections is penicillin, with cephalosporins or macrolides as alternatives in the penicillin-allergic patient.

Neisseria Meningitidis

N Meningitidis **(meningococcus) can cause an acute, life-threatening infection,** often associated with a rash. Meningococcemia causes a severe illness with high fevers, hypotension, and altered mental status. Most people with meningococcemia progress to develop frank meningitis, with its associated signs of meningeal irritation. The **rash of meningococcemia often starts as an erythematous maculopapular eruption that progresses to form petechiae.** The petechiae may coalesce into purpura in a condition known as purpura fulminans that can result in gangrene and amputation of limbs. Other complications include disseminated intravenous coagulation (DIC), adrenal hemorrhage, deafness, and cerebral and renal infarctions.

Someone with suspected meningococcemia should be immediately hospitalized, usually in the intensive care unit. The ABCs (Airway, Breathing, and Circulation) should be urgently evaluated, blood and cerebrospinal fluid cultures collected, and empiric antibiotic therapy instituted until an organism is grown out and drug sensitivities are obtained. A common empiric regimen for presumed meningitis in infants less than 30 days old is ampicillin plus gentamicin while for adults vancomycin plus ceftriaxone may be used. Antibiotic coverage can be later narrowed based on culture results. The first choice for proven meningococcal meningitis is penicillin G. A meningococcal vaccine is now recommended for routine childhood immunization and also should be offered to patients at risk for the disease (asplenic, those living in dormitories or military barracks). Close contacts of someone with meningococcal infection should be offered prophylaxis with ciprofloxacin or rifampin.

TICK-BORNE DISEASES

Rocky Mountain Spotted Fever

Rocky Mountain spotted fever (RMSF) is an acute, life-threatening infection caused by the organism *Rickettsia rickettsii*, which is transmitted via various species of tick. The infection occurs more often in the summer months, when people are more likely to be outdoors. Despite its name, RMSF is most common in the southeastern United States. The illness causes acute fever, headache, myalgias, and fatigue. The **classic exanthem is a macular, papular, or petechial eruption that starts on the wrists and ankles and includes the palms and soles.** Laboratory tests often show a low white blood cell count, low platelet count, hyponatremia, and elevated liver enzymes. The diagnosis is confirmed with serology, but this is not helpful in the acute setting. Due to its severity, a high suspicion for RMSF should be maintained and likely cases of the illness treated empirically with doxycycline.

Lyme Disease

Lyme disease is endemic in many areas of the United States, including New England and the mid-Atlantic regions. The causative spirochete, *Borrelia burgdorferi*, is transmitted via the bite of ticks of the *Ixodes* species. Because the tick is very small, infected persons are often unaware of a history of a tick bite. The characteristic rash, **erythema migrans,** develops 3 to 30 days following infection. The exanthema is typically an expanding erythematous macule with central clearing, often described as appearing like a "bull's-eye." Early dissemination of the disease can present as multiple secondary erythema migrans, Bell's palsy, aseptic meningitis, and carditis and rarely as complete heart block. Late disease is most characteristically marked by arthritis. The treatment of choice for Lyme disease is doxycycline and the diagnosis can be confirmed with serologic studies. Table 48-1 provides a summary of some of the most common causes of the presentation of rash and fever in children.

Table 48–1 INFECTIOUS CAUSES OF FEVER AND RASH

DISEASE	CAUSATIVE ORGANISM	RASH	OTHER SYMPTOMS
Roseola	HHV-6	Erythematous, maculopapular rash, starting on the trunk and sparing the face	Prodromal high fever
Chicken pox	Varicella-Zoster virus	Papules or vesicles on an erythematous base "dew drops on a rose petal"	Fever and malaise
Shingles	Varicella-Zoster virus	Vesicular rash in a dermatomal pattern	Postherpetic neuralgia
Erythema infectiosum	Parvovirus B19	Erythematous macular rash on cheeks "slapped cheek," followed by a lacy, reticulated rash over trunk and extremities	Prodromal fever and URI symptoms, arthritis in adults
Measles	Measles virus	Erythematous maculopapular rash starting at the forehead and moving down the body	Koplik spots, fever, and malaise
Rubella	Rubella virus	Erythematous macular rash starting at the face and neck and moving to the trunk and extremities	Prodromal fever, sore throat, and malaise; congenital rubella syndrome
Small pox	Variola virus	Macules, papules, or pustules at the same stage of development	Fever, myalgias, and malaise

(*Continued*)

Table 48–1 INFECTIOUS CAUSES OF FEVER AND RASH (CONTINUED)

DISEASE	CAUSATIVE ORGANISM	RASH	OTHER SYMPTOMS
Hand-foot-and-mouth disease	Coxsackie virus	Vesicular enanthem on tongue, lips and in mouth; maculovesicular rash on hands, feet, buttocks, and groin	Fever
Scarlet fever	Group A *Streptococcus*	Erythematous papular rash starting on neck and moving to trunk and extremities, "strawberry tongue" enanthem	Pharyngitis and fever
Rheumatic fever	Group A *Streptococcus*	Erythema marginatum-erythematous, serpiginous macules with pale centers	Carditis, polyarthritis, subcutaneous nodules and Sydenham chorea
Meningococcemia	*Neisseria meningitidis*	Erythematous maculopapular rash progressing to form petechiae	Meningitis, fever, myalgias, hypothermia, and hypotension
Toxic shock syndrome	*Staphylococcus aureus*	Diffuse erythematous macular rash with peeling palms and soles	Fever, vomiting, diarrhea, and hypotension
Typhoid fever	*Salmonella enterica*	Maculopapular rash on lower chest and abdomen "rose spots"	Fever, myalgias, diarrhea, abdominal pain, and hepatosplenomegaly

Table 48–1 INFECTIOUS CAUSES OF FEVER AND RASH (CONTINUED)

DISEASE	CAUSATIVE ORGANISM	RASH	OTHER SYMPTOMS
Rocky Mountain spotted fever	*Rickettsia rickettsii*	Maculopapular rash starting on the wrists and ankles and involving the palms and soles	Fever, headache, myalgias, and malaise
Lyme disease	*Borrelia Burgdorferi*	Erythema migrans-erythematous macule with central clearing "bull's-eye"	Malaise, Bell's palsy, meningitis, arthritis, carditis, and heart block
Ehrlichiosis	*Anaplasma phagocytophilum, Ehrlichia chaffeensis*	Erythematous maculopapular rash	Fever, headache, myalgias, nausea, and vomiting

Comprehension Questions

48.1 A 4-year-old boy is brought to your office by his mother for a rash on his face that the mother first noticed the day before. His mother comments that it looks like somebody "slapped him." The mother reports that he has had a cold for the last couple of days. The child's physical examination is unremarkable except for a erythematous macular rash over both cheeks. The mother admits that the child is behind on his immunization schedule. Which of the following is the most likely cause?

A. Varicella-Zoster virus
B. Parvovirus B19
C. Human herpes virus 6
D. Rubella virus
E. Child abuse and you should contact social services immediately

48.2 A 6-year-old girl is brought to your office by her mother because of a rash. The mother first noticed the rash 1 day ago. The mother reports that several kids in the child's school have come down with chicken pox but that the child has received all of her immunizations including two doses of the varicella vaccine. You observe the child actively playing with the toys in your waiting room before both the mother and child are brought back. The child has a temperature of 100.4°F (38.0°C), a pulse of 90 beats/min, a blood pressure of 100/70 mm Hg, and a respiration rate of 20 breaths/min. The physical examination is unremarkable except for 20 vesicles on erythematous bases sparsely scattered on the child's trunk and limbs. Which of the following is the most likely diagnosis?

A. Chicken pox
B. Measles
C. Roseola
D. Rocky Mountain spotted fever
E. Shingles

48.3 You are on duty when an 18-year-old adolescent male is brought to the emergency room from his college dorm. He is confused and cannot give a history. He has a temperature of 104.0°F (40.0°C), pulse of 110 beats/min, blood pressure of 90/60 mm Hg, and a respiration rate of 24 breaths/min. His head cannot be moved because of nuchal rigidity. Multiple petechiae are observed on his buttocks and legs. The patient's dorm mates who brought him to the ER ask you what they should do. Which of the following describes the most appropriate advice that you should give to the patient's dorm mates?

A. Go home and get some rest.
B. Take acyclovir for prophylaxis.
C. Take penicillin for prophylaxis
D. Take rifampin for prophylaxis.
E. Check themselves into the hospital immediately.

48.4 A 7-year-old boy is brought to a hospital in Charlotte, North Carolina with a fever of 104.0°F (40.0°C). A maculopapular rash is seen on his wrists and ankles but the palms and soles are spared. His lab results show leukopenia, hyponatremia, and elevated liver enzymes. His parents say that he was on a camping trip 1 week ago but they vigorously used bug sprays and filtered all of their water. His father came in contact with poison oak but the boy denies any pruritus. Which of the following antibiotics is the best treatment?

A. Penicillin
B. Acyclovir
C. Ceftriaxone
D. Vancomycin
E. Doxycycline

ANSWERS

48.1 **B.** This question describes erythema infectiosum, or fifth disease, which is caused by parvovirus B19. It often has a prodrome of fever and upper respiratory systems mistaken by the mother in this question as a "cold." This child also has the classic "slapped cheek" rash of erythema infectiosum and, while the child does need to be caught up on his immunizations, the child has the classic symptoms of fifth disease and not of the diseases for which children are immunized.

48.2 **A.** The child has chicken pox caused by the Varicella-Zoster virus. While the child did received two doses of the varicella vaccine and the vaccine is effective, sporadic breakthrough cases do occur. However, the cases are usually much less severe and have fewer complications than in unimmunized patients.

48.3 **D.** The patient has meningitis and meningococcemia caused by *N meningitidis*. The patient is severely affected and is in septic shock. All people in close contact with the patient should receive ciprofloxacin or rifampin prophylaxis.

48.4 **E.** The patient has Rocky Mountain spotted fever. The disease is commonly found in North Carolina and is carried by ticks that the boy could have picked up during the camping trip. RMSF has a characteristic rash that starts on the wrists and ankle and can eventually involve the palms and soles. Typically, the rash of RMSF spreads centripetally from the wrists and ankles to involve the trunk and extremities.

Clinical Pearls

- Shingles that approaches the eye, because of a reactivation involving the trigeminal nerve, should be evaluated by an ophthalmologist. A clue that the eye may become involved is seeing characteristic lesions approaching the tip of the nose.
- Many vaccine-preventable illnesses, including measles, rubella, and varicella, have characteristic rashes associated with them. Always get a vaccination history on children presenting with fever and rash. Also, consider the possibility that immigrants from other countries may not be vaccinated if they present with similar symptoms.

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Case 49

A 32-year-old woman presents for evaluation of a lump that she noticed in her right breast on self-examination. She says that she does not examine herself often, but that she thinks that this lump is new. She has not had any nipple discharge and has no breast pain, although the lump is mildly tender on palpation. She has never noticed any masses before and has never had a mammogram. She has no history of breast diseases and has never had a biopsy. There is no history of breast cancer in the family. She takes oral contraceptive pills regularly, but no other medications. She does not smoke cigarettes or drink alcohol. She has never been pregnant. On examination, she is a well-appearing, but somewhat anxious, thin woman. Her vital signs are within normal limits. Her general physical examination is normal. Examination of her breasts reveals no skin dimpling or retraction and no nipple discharge. In the lower outer quadrant of the right breast there is a 2-cm, firm, well-circumscribed, movable mass that is mildly tender. No other masses are felt, but the breast tissue is noted to be firm and glandular throughout. No axillary, supraclavicular, or cervical lymphadenopathy is appreciated.

- What is the most likely diagnosis of this breast lesion?
- What is the next step in evaluation?
- What is the recommended follow-up for this patient?

ANSWERS TO CASE 49:
Breast Diseases

Summary: A 32-year-old woman presents for evaluation of a lump in her right breast that she found on breast self-examination (BSE). The lump is found to be 2 cm in size, firm, and mobile. No adenopathy is noted.

- **Most likely diagnosis:** Breast cyst.
- **Next step in evaluation:** Needle aspiration of cyst.
- **Follow-up:** If aspiration of the cyst results in complete resolution of the mass, and if the fluid is clear/yellow, follow-up clinical examination in 1 to 2 months to ensure no recurrence; if aspiration does not make the mass disappear, if the fluid is bloody, or if the lesion recurs, further evaluation with biopsy of the lesion is indicated.

ANALYSIS

Objectives

1. Learn how to workup a breast mass.
2. Know the risk factors for breast cancer.
3. Know how to manage benign breast diseases.

Considerations

A palpable breast mass is a potentially frightening finding for a woman. The media has widely disseminated the statistic that 1 in 8 women will have breast cancer in their lifetime. Consequently, the evaluation of the breast mass is designed to answer the one question that is on the patient's mind, whether she says it or not: Is this lump breast cancer? Fortunately, most palpable breast masses are not cancerous. Unfortunately, a definitive determination of whether a lesion is benign or malignant cannot be made by history and physical examination findings only.

Certain factors have been identified as increasing a woman's risk of breast cancer. A family history of breast cancer in a first-degree relative (parent, sibling), especially if the cancer occurred in a premenopausal woman and was bilateral, is associated with an increased risk. Early age at menarche (<12 years), late age of menopause (>55 years), and nulliparity or first live birth after the age of 30 years are also associated with higher risks. The use of hormones, either estrogen alone or combined with progesterone, are considered to confer higher risks, although recent studies question whether oral contraceptives pose any significant risk. Lifestyle considerations, including obesity, physical

inactivity, and alcohol use (>3 drinks per day), also are identified risk factors. Finally, a history of previous breast disease, especially biopsies showing atypical hyperplasia, carcinoma in situ, or prior breast cancer, are associated with increased risks.

In the case presented, there are several pieces of information presented that lead toward a likelihood of a benign process. Breast cancer can occur at any age, but approximately 70% of breast cancers occur in women older than age 50 years. You can never overlook the possibility of malignancy in a woman who is in her thirties, but the possibility of cancer is lower in her than in an older woman. The characteristics of the lesion are also more consistent with a benign, probably cystic, process. It is described as well-circumscribed, firm, mobile, tender, and with no overlying skin changes. Lesions that are hard, fixed in place, nontender, have indistinct borders, or have overlying skin dimpling/retraction are more suggestive of cancer. Nevertheless, no individual characteristic on examination is diagnostic and an appropriate evaluation is necessary.

APPROACH TO
Diseases of the Breast

DEFINITIONS

ACROMEGALY: A condition that results from the excessive production of growth hormone by a pituitary adenoma. Among the numerous physical effects of the excessive growth hormone, menstrual irregularities and breast discharge may result.

DUCT ECTASIA: Inflammation of a mammary duct below the nipple, which can lead to duct obstruction, a tender mass, and duct discharge.

INTRADUCTAL PAPILLOMA: A benign tumor growth into a mammary duct, often with a resultant palpable small mass and duct discharge.

CLINICAL APPROACH

Palpable Breast Mass

Following a complete history, with an emphasis on factors that may confer an increased risk of cancer, a careful examination of both breasts should be performed. The breast examination should include a visual inspection for skin changes, dimpling, retraction, and asymmetry, and should note the presence and quality of any nipple discharge (color, presence of blood, etc).

Examination by palpation should be performed in a systematic manner to include all quadrants of the breast, as well as the superficial, intermediate, and

deep breast tissue. Specific characteristics of any palpable lumps, including size, location, tenderness, mobility, firmness, and distinction of the mass from the surrounding tissue, should be noted, both to assist in developing a diagnosis and to allow for serial examinations to determine if the mass is changing. The breast examination should also include palpation of the axilla and supraclavicular regions to identify the presence of enlarged lymph nodes. The characteristic of the mass and the age of the women will provide initial clue into likely diagnosis (see Table 49–1).

The identification of a new breast solid mass particularly in women older than 35 years should prompt **triple assessment, which includes a clinical breast examination, imaging (mammography), and pathology assessment either by core biopsy or surgical excision.**

For women younger than 35 years of age, suspected lesions characteristic of fibroadenoma or fibrocystic changes can be assessed by ultrasonography, rarely mammography followed by fine-needle aspiration with histological evaluation. **Ultrasonography** can be used as an adjunct to mammography in an effort to determine if the lesion is solid or fluid filled. It can also be used in women with denser breast or women with persistent breast pain without evidence of mass by mammography.

Fine-needle aspiration (FNA) can be both diagnostic and therapeutic. A FNA that identifies fluid that is clear, yellow, or green-tinged and that results in complete resolution of a mass is diagnostic of a benign cyst. In this setting, the fluid can be discarded and no further workup is necessary. The patient should be seen in follow-up in 4 to 6 weeks for reexamination to evaluate for recurrence of the lesion.

If the mass does not completely resolve, if the fluid withdrawn is bloody, if no fluid is aspirated, if the lesion is found to recur on follow-up, or has complex nature (containing cystic and solid components), then further evaluation

Table 49–1 TYPICAL CHARACTERISTICS OF BREAST LUMPS ON PHYSICAL EXAMINATION

CHARACTERISTIC	MORE LIKELY BENIGN	SUSPICIOUS FOR MALIGNANCY
Consistency	Soft	Firm/hard
Surface	Smooth, regular	Irregular
Mobility	Mobile	Fixed or tethered
Symptoms	Tender	Painless
Age	<30 y	>50 y

Data from Lippman ME. Breast cancer. In: Fauci AS, Braunwald E, Kasper DL, et al, eds. Harrison's Principles of Internal Medicine. *17th ed. New York, NY: McGraw Hill Medical; 2008:564.*

is indicated by stereotactic core-needle or excisional biopsy. Several biopsy techniques are used in practice. FNA can be performed on solid lesions; however it should be used for lesions most likely to be cystic. It is the least invasive and simplest procedure, but also has the highest risk of false-negative or nondiagnostic results. **Core-needle** biopsy and **mammotome** biopsy use larger cutting needles to obtain larger tissue samples. These are usually performed using ultrasound or mammographic guidance by a radiologist or surgeon. These procedures have a higher chance of providing a diagnostic sample but are more invasive and costlier than FNA. Although **surgical excision** is the most invasive and expensive diagnostic method, it is indicated in stereotactic biopsies showing **atypical ductal hyperplasia** and is also therapeutic by removing the lesion in question.

Breast Pain

Breast pain (mastalgia) is the most frequent breast-related complaint for which women present for evaluation. The etiology of chronic mastalgia is often unknown. As with the presentation of a breast lump, the patient's primary fear, whether spoken or unspoken, is whether the pain is a manifestation of breast cancer. As such, the evaluation should include a history to evaluate for high breast cancer risk status, a careful breast examination, and a screening mammography in women for whom it is routinely indicated. Any abnormalities found in the primary evaluation should be workedup as appropriate. **Breast pain is not a common presentation of breast cancer,** particularly when it is bilateral breast pain.

Most breast pain may be categorized as cyclic mastalgia, noncyclic mastalgia, or nonmammary pain. **Cyclic mastalgia** is usually diffuse, bilateral often radiating to axilla and arm and related to the woman's menstrual cycle. Pain occurs during late luteal phase and resolves with onset of menses. In some cases, it can be unilateral. **Noncyclic mastalgia** may be continuous or intermittent, but is not associated with the menstrual cycle. It is more commonly unilateral and more prevalent in postmenopausal women. **Nonmammary pain** is breast pain secondary to another etiology. This is often chest wall pain but, sometimes, the underlying cause may be difficult to determine.

Common Causes of Mastalgia

Etiology of most mastalgia unknown. Common causes of mastalgia are:

- Pregnancy
- Mastitis
- Thrombophlebitis
- Cyst
- Benign tumors
- Cancer
- Musculoskeletal cause

- Stretching of Cooper ligaments
- Pressure from brassiere
- Fat necrosis from trauma
- Hidradenitis suppurativa
- Medications such as OCPs, antidepressants, antipsychotics, antihypertensive, and others

Laboratory testing is usually unnecessary in the evaluation of mastalgia, although a pregnancy test should be performed in reproductive-age women. Hormonal contraceptives or hormone replacement therapy may be causes of breast pain and consideration should be given to discontinuation or reduction of estrogen dosages. An appropriately fitted supportive bra and lifestyle changes, such as tobacco cessation, and stress reduction techniques, are often successful in alleviating symptoms. Evening primrose oil, caffeine reduction, and vitamins have not been shown to provide much relief. Topical NSAIDs have shown the most promise. For women with unrelenting pain in spite of the above modifications, **danazol,** an antigonadotropin, is Food and Drug Administration (FDA) approved for the treatment of breast pain, but is relatively expensive and has numerous side effects (hair loss, acne, weight gain, and irregular menses).

Nipple Discharge and Galactorrhea

Nipple discharge is usually caused by a benign process. Up to 25% of women will have this symptom during their life. Nipple discharge that occurs only with nipple stimulation, that is clear, yellow, or green, and that appears from multiple ducts is usually physiologic. This discharge often goes away if efforts are made to reduce nipple stimulation (including ceasing efforts to check to see if the discharge will still occur).

Discharge that is spontaneous, persistent, bloody, from a single duct, and associated with a mass is more likely to represent a pathologic process. In this setting, the most common causes are intraductal papillomas, duct ectasia, cancers, and infections. If the discharge is not obviously bloody, a fecal occult blood test card can be used to test for occult blood.

Following the initial history and physical examination, mammography should be performed in all women with a spontaneous or bloody discharge, and in any woman in whom routine mammographic evaluation is indicated. Palpable breast masses should be appropriately evaluated. The **treatment of most unilateral, spontaneous, or bloody nipple discharges is surgical excision of the terminal duct** involved. This both resolves the problem and allows for pathologic diagnosis of the problem**.**

Galactorrhea is a discharge of milk or a milk-like secretion from the breast in the absence of parturition or beyond 6 months postpartum in a non–breast-feeding woman. The secretion may be a milky or serous (yellow) appearing, intermittent or persistent, scant or abundant, free-flowing or expressible, and unilateral or bilateral. If the clinician is unsure if the discharge is galactorrhea,

the discharge can be sent off for staining and microscopic analysis. Galactorrhea will contain few cells and will have fat globules. The condition is more common in women who are 20 to 35 years of age and in previously pregnant women.

Galactorrhea is associated with stress, physical irritation, numerous medications, hypothyroidism, chronic renal failure, hypothalamic-pituitary disorders, hormone-secreting neoplasms (most commonly pituitary adenomas), or may be idiopathic but is **not** associated with breast cancer.

Numerous pharmacologic agents are causes of galactorrhea. These agents can block dopamine and histamine receptors, deplete dopamine stores, inhibit dopamine release, and stimulate lactotrophs. Common medications and classes of medications associated with galactorrhea include: SSRIs, TCAs, atenolol, verapamil, antipsychotics, H_2 histamine blockers (cimetidine), and opiates, to name a few. Estrogen in oral contraceptives can cause galactorrhea by suppressing the hypothalamic secretion of prolactin inhibitory factor and by direct stimulation of the pituitary lactotrophs.

Offending medications should be discontinued, if possible. Prolactin and thyroid-stimulating hormone levels should be drawn to evaluate for endocrine abnormalities. Assessing electrolytes and renal function can assess for renal failure, Cushing disease, and acromegaly. Imaging of the pituitary to evaluate for a pituitary adenoma with magnetic resonance imaging (MRI) is indicated if the prolactin level is significantly elevated.

Treatment is geared at addressing the underlying condition, that is, hypothyroidism should be treated with hormone replacement. It is also geared toward severity of the prolactin level and pending fertility status.

Dopamine agonists are the treatment of choice in most patients with hyperprolactinemic disorders. Bromocriptine is the preferred agent for treatment of hyperprolactin-induced anovulatory infertility. Surgical resection rarely is required for prolactinomas.

Comprehension Questions

49.1 A 34-year-old woman notes that she has had breast nipple discharge for 2 months. A urine pregnancy test is negative. She was on antipsychotic medication for a history of schizophrenia, but has not taken the medication in 6 months. Labs reveal normal TSH, T3, and T4 and the thyroid is not palpable. The physician makes an assessment that the circumstances and characteristics are likely associated with a pathologic process. Which of the following characteristics is most concerning?

A. Yellow
B. Bilateral
C. Bloody
D. Present with nipple stimulation

49.2 A 52-year-old woman has a palpable breast lump. An attempt at FNA does not result in aspiration of fluid. A mammogram is read as normal. Her mother was diagnosed with breast cancer at age 45. She does not smoke but socially drinks alcohol. She currently uses low-dose estrogen contraception pills and takes 1200 mg of calcium daily. She began her menstrual periods at age 10 and she had her first child at age 24. Which of the following is the appropriate next step?

A. Repeat clinical examination in 4 to 6 weeks.
B. Repeat mammogram routinely in 1 year.
C. Referral for biopsy.
D. Discontinuation of her hormone replacement therapy.

49.3 A 29-year-old woman comes in to the clinic with complaints of left-sided nipple discharge. On further questioning she states that the discharge is milky in color. She is a G2P2 with the last birth $3^1/_2$ years ago. She breast-fed both children for 9 months. She is on no medications and is having regular menstrual periods. You express a small amount of nonbloody milky discharge from several ducts from the left nipple and are unable to express discharge from the right. Which of the following is the best diagnostic step?

A. Send for diagnostic mammogram. If negative, reassure that the discharge is not significant.
B. Refer to a breast specialist for evaluation for unilateral nipple discharge.
C. Obtain TSH, free T4, and prolactin levels.
D. Obtain levels of FSH, LH, and GnRH.

ANSWERS

49.1 **C.** Nipple discharges that are spontaneous, unilateral, persistent, bloody, and associated with a mass are more likely to represent pathologic processes. Most of these are still benign (eg, papilloma, duct ectasia), but evaluation and surgical intervention are usually required.

49.2 **C.** A biopsy is the next appropriate step in this setting. A negative mammogram is not diagnostic of a benign process and does not rule out the possibility of having a breast cancer. A tissue diagnosis is needed in this setting especially with a known first-degree relative with breast cancer and early age of menarche.

49.3 **C.** The evaluation and management of most cases of galactorrhea can be handled by the primary care physician. If pituitary adenoma is diagnosed then the patient can be referred for specialty care. Milky discharge, galactorrhea, from multiple ducts in the nonlactating breast may occur in certain syndromes—it is usually due to an increased secretion of pituitary prolactin. A pregnancy test should be the first evaluation. Hypothyroidism can also cause hyperprolactinemia. Psychiatric agents such as chlorpromazine and estrogen containing agents such as the oral contraceptive pills may also cause milky discharge.

Clinical Pearls

- Approximately 1% of breast cancer occurs in men. A new palpable mass in a man's breast should prompt a diagnostic evaluation.
- Remember that the question in the mind of just about every woman presenting with a breast-related complaint is, "Do I have breast cancer?" The job of the physician is to both manage the presenting complaint and to answer this question.

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Case 50

A 28-year-old nulliparous woman presents for evaluation of irregular menstrual cycles for the past year. Her periods come only every 2 or 3 months and she has gone as long as 4 months without a period. Currently, she gives a last menstrual period of 11 weeks ago. She says she had menarche at age 13 years and that her cycles have been "mostly" regular, usually occurring every 30 days, but she would miss a cycle several times a year. She has never been on hormonal contraception. She does not smoke, does not drink alcohol, and does not exercise. She is sexually active with a single partner and uses condoms for contraception. On review of systems, she reports a 30-lb weight gain in the past 18 months, but otherwise has felt fine. On examination, she is noted to be obese, with a body mass index of 30. Her vital signs are otherwise normal. She has fine hair growth on her face and a velvety thickening of the skin on her neck. Her general physical examination is normal. A pelvic examination reveals normal external genitalia, no vaginal or cervical discharge, no cervical motion tenderness, and no uterine or adnexal masses.

- What is the most likely diagnosis?
- What is the first laboratory test that should be performed?
- What therapy can best regulate her menstrual cycle?

ANSWERS TO CASE 50:
Menstrual Cycle Irregularity

Summary: A 28-year-old woman presents for evaluation of irregular menstrual cycles for the past year. She is obese and noted to have gained 30 lb. She is found to be hirsute and to have acanthosis nigricans. Her pelvic examination is normal.

- **Most likely diagnosis:** Anovulatory menstrual cycles secondary to polycystic ovarian syndrome (PCOS)
- **Initial laboratory test:** Pregnancy test
- **Treatment to regulate cycle:** Oral contraceptive pills

ANALYSIS

Objectives

1. Learn some of the common causes of irregular menstrual cycles.
2. Develop an understanding of a rational workup of menstrual cycle abnormalities.
3. Learn the management of common menstrual cycle disorders.

Considerations

Menstrual cycles are considered normal if they occur at regular intervals of 21 to 35 days in length. During their reproductive years, most women will, at some point, have late or missed menstrual cycles. When this occurs on a rare occasion and pregnancy is ruled out, watchful waiting is usually indicated, with resumption of normal menstrual cycles almost always occurring.

The differential diagnosis of persistent menstrual cycle irregularities is broad. Pregnancy must be ruled out in any menstrual pattern change. After pregnancy is excluded, numerous neuroendocrine and genitourinary conditions must be considered.

In a normal (highly simplified) menstrual cycle, the hypothalamus secretes GnRH, which stimulates the anterior pituitary to secrete FSH and LH. As the FSH level rises, it causes an ovarian follicle to mature and it to release estrogen which induces endometrial proliferation. A mid-cycle LH surge causes ovulation, and the follicle is transformed into the corpus luteum that secretes progesterone, which compacts and matures the endometrium. If pregnancy does not occur, the production of progesterone abruptly decreases, resulting in sloughing of the endometrium and a menstrual bleed.

In the case presented of an obese, hirsute woman with ongoing weight gain and irregular menses, PCOS should be the initial consideration (after pregnancy). PCOS is a syndrome of insulin resistance and androgen excess. It is associated with infertility, hirsutism, acne, obesity, and metabolic syndrome. Diagnosis is made by having two of the three factors: hyperandrogenism, chronic anovulation, and polycystic ovaries on ultrasound. **Anovulation is the menstrual cycle irregularity associated with PCOS.** Without ovulation, there is a failure of luteal production of progesterone, resulting in an absence of normal menstruation. Hyperandrogenemia can be tested for by measuring serum total testosterone and sex hormone binding protein and calculating the free serum testosterone. Women with PCOS can have induced menstrual bleeds by providing periodic supplemental progesterone or by using oral contraceptive pills. Weight loss is very important to increase fertility; even a loss of 2% to 5% can greatly increases rates of success. The insulin resistance in PCOS is treated with metformin and thiazolidinediones. PCOS caused infertility is treated with clomiphene citrate, aromatase inhibitors, and gonadotropins.

APPROACH TO Menstrual Cycle Irregularity

DEFINITIONS

AMENORRHEA: Absence of menstrual bleeding for 6 or more months when a woman is not pregnant.

MENOMETRORRHAGIA: Heavy menstrual flow or prolonged duration of flow occurring at irregular intervals.

MENORRHAGIA: Excessive menstrual flow, or prolonged duration of flow (>7 days), occurring at regular intervals.

METRORRHAGIA: Bleeding occurring at irregular intervals.

CLINICAL APPROACH

A thorough history is the initial component of the evaluation of menstrual irregularities. The history of presenting complaint should examine both the specific abnormality that is occurring and when it was first noted. A menstrual calendar can be very valuable in this setting. Associated symptoms, including weight gain or loss, galactorrhea, heat or cold intolerance, and other forms of bleeding should be documented. A complete general health history is necessary. A complete reproductive health history, including age at menarche, history of any previous menstrual cycle abnormalities, medications (especially anticoagulants, phenytoin, antipsychotics, TCAs, and steroids), contraception, infections, surgeries, and sexual practices along with pregnancies

and their outcomes is required. A social history focusing on stressors, substance use, exercise, eating habits, and sexual activity can provide important information.

The general physical examination should attempt to identify medical conditions that can cause menstrual abnormalities. Extremes of body mass index—both overweight and underweight—can affect menstruation. Hirsutism or acne suggests androgen excess. The thyroid should be examined for size, consistency, and the presence of nodules. Skin and hair changes may also occur with thyroid conditions. Breasts should be examined for galactorrhea. Unexplained bruising or easy bleeding may occur with coagulopathies.

The pelvic examination is a critical component. In women having excessive or unusual bleeding, initial efforts should be made to determine whether the blood is coming from the uterus or another anatomic site. Urethral, rectal, vaginal wall, or cervical bleeding can easily be mistaken for menstrual abnormality. Signs of infection should be noted and cultures collected, as cervicitis may predispose to cervical bleeding. A Papanicolaou (Pap) smear should be performed. Bimanual examination should note the size and consistency of the uterus, the presence of any masses or tenderness. The adnexa should also be carefully examined for abnormality.

Abnormal Bleeding Associated with Regular Menstrual Cycles

Menorrhagia with regular intervals between bleeding is suggestive that regular ovulation is occurring. This implies that the endocrine pathways are functioning normally and that the problem may be anatomic within the genital or hematologic system. **Leiomyomata** (fibroids), especially those that are submucosal in the uterus, are a common cause of this problem. They create an increased endometrial surface area with a resultant increase in menstrual bleeding. **Endometrial polyps** may cause menorrhagia by a similar mechanism. **Coagulopathy that is inherited (most commonly von Willebrand disease) or due to medications (eg, warfarin) is a common cause. Also, liver disease or thrombocytopenia may contribute.**

Reduced volume of menstrual bleeding associated with regular ovulation is a less common occurrence. **Asherman syndrome** is a scarring within the uterine cavity caused by trauma from uterine curettage. It can result in reduction in the size of the uterus as the walls become scarred to each other. This may cause minimal or even absent menstruation in the face of normal hormonal function. A scarred and obstructed cervical os can cause a similar picture.

Abnormal Bleeding Associated with Irregular Menstrual Cycles

Bleeding that is unpredictable in terms of timing and flow is known as dysfunctional uterine bleeding (DUB) and generally implies an abnormality

within the hypothalamic-pituitary-ovarian axis. This pattern is common shortly after menarche and as a woman approaches menopause. At other times, it signals anovulation. In this setting, the endometrium is continuously stimulated by estrogen and sloughs off irregularly. Chronic anovulation should be evaluated with prolactin and LH serum levels.

Continuous estrogen stimulation can also lead to endometrial hyperplasia and endometrial carcinoma. **Risk factors for endometrial carcinoma include a history of anovulatory menstrual cycles, obesity, nulliparity, older than age 35 years, the use of tamoxifen, or of unopposed exogenous estrogen.**

The **evaluation of a woman with DUB is dependent on age and risk factors.** In the period after menarche, watchful waiting is usually indicated, with correction of the problem usually occurring within 1 to 2 years. In women younger than 35 years who are not at increased risk of endometrial cancer, treatment may be offered without workup beyond the history and physical examination.

Further evaluation is indicated for women with risk factors for endometrial cancer, women younger than age 35 years with continued symptoms in spite of treatment, and postmenopausal women with uterine bleeding. The workup involved typically includes imaging of the pelvic organs with an ultrasound and an endometrial biopsy. **Transvaginal pelvic ultrasound** provides information on uterine size and masses, and can assess the thickness of the endometrium, which correlates with the risk of hyperplasia. An **endometrial biopsy** can be performed quickly and easily in the office setting, using a thin, disposable, sampling device. The combination of sonographic measurement of endometrial thickness and endometrial biopsy is highly sensitive for the diagnosis of endometrial cancer. **Hysteroscopy** (endoscopic evaluation of the uterine cavity) can directly visualize endometrial masses, polyps, or other abnormalities, and can lead to directed biopsy. It is often performed with **dilation and curettage** (D&C), which sharply removes almost the entire endometrial lining for diagnostic and therapeutic purposes.

When the workup does not reveal malignancy, **anovulatory bleeding is usually responsive to treatment with either combined estrogen and progestin oral contraceptives (OCPs) or progestin alone.** A progestin can be given for 7 to 10 days with a subsequent withdrawal bleed expected to occur within a week following the completion of the course. Both of these regimens reduce the risk of developing endometrial hyperplasia and carcinoma. When medical treatments fail, or when symptoms are severe, surgical options may be required. Hysterectomy provides definitive treatment and is necessary in the case of a malignancy. Endometrial ablative procedures are also available and widely used.

Comprehension Questions

50.1 A 42-year-old obese G2P2 woman presents for evaluation of irregular menstrual bleeding for a year. She has had painless vaginal bleeding in various amounts at various times of the month. She has a history of smoking half a pack of cigarettes per year for 10 years. She has two children, is on no medications, and has no significant medical history. She had been taking the oral contraceptive agent for 5 years during her teen years. Her examination reveals her uterus to be slightly enlarged, but without masses or tenderness. The remainder of her examination is normal. A pregnancy test is negative. Which of the following is the most significant risk factor for her having endometrial cancer?

A. Smoking
B. Parity
C. Body habitus
D. History of oral contraceptive use

50.2 A 35-year-old woman has had irregular periods since high school. She frequently misses cycles and has never been pregnant. When she has periods they are very light and last only a few days. She still has some acne and is noted to have some hair growing under her chin. She denies taking any medications or history of other gynecologic or medical problems. Which of the following is the most appropriate evaluation for the initial workup of her problem?

A. Thyroid-stimulating hormone (TSH)
B. Serum karyotype
C. Free estrogen
D. Urine cortisol

50.3 A 28-year-old woman is complaining of spotting irregularly between periods for the past 2 months. She has been previously healthy and never pregnant. She has been sexually active for the past 6 months. On examination her only positive findings are a mildly enlarged and moderately tender uterus. Her pregnancy test is negative. Which of the following is the most probable diagnosis?

A. Uterine leiomyoma
B. Cervical carcinoma
C. Endometritis
D. Endometrial cancer

ANSWERS

50.1 **C.** This patient's obesity is the most significant risk factor for endometrial cancer. Parity is protective for endometrial cancer. Risk factors for endometrial cancer include anovulatory menstrual cycles, obesity, nulliparity, age greater than 35 years, and use of tamoxifen or unopposed exogenous estrogen. Interestingly smoking is a negative risk factor for endometrial cancer.

50.2 **A.** Estrogen does not have a role in the initial workup for anovulation; serum karyotype is useful for premature ovarian failure but not for anvoluation. Urine cortisol may help in the diagnosis of Cushing's disease, but not generally indicated unless the patient has other stigmata of corticosteroid excess such as abdominal striae, easy brusability, and buffalo hump. TSH is indicated in DUB workup. Both total serum testosterone levels and prolactin are useful. Thus, in general, a pregnancy test, TSH and prolactin level are the initial tests for the evaluation of menstrual irregularities.

50.3 **C.** Endometritis is a common cause of vaginal spotting. It is generally a polymicrobial infection caused by an ascending infection of normal vaginal flora. Commonly isolated organisms include gonorrhea, *Chlamydia*, *Ureaplasma urealyticum*, *peptostreptococcus*, *Gardnerella vaginalis*, and the group B *Streptococcus species*. The patient's history makes cervical cancer less likely. Leiomyoma or polyps are possible, but less likely with her history of recent spotting and sexual activity. Endometrial cancer would also be unlikely in a patient with previously regular menses. The diagnosis of endometritis can be confirmed with endometrial biopsy showing inflammatory cells, in particular plasma cells.

Clinical Pearls

- The first test performed on a woman with menstrual cycle irregularities should be a pregnancy test.
- A history of anovulatory cycles does not confer absolute protection against pregnancy. Ovulation may occur intermittently and irregularly. If the woman does not want to become pregnant, she should be counseled on contraceptive options.

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Case 51

A 30-year-old woman presents to your office with the chief complaint of a "yeast infection that I can't seem to shake." She also has noticed that she has been urinating more frequently, but thinks that it is related to her yeast infection. Over the last several years she has noticed that she has gained more than 40 lb. She has tried numerous diets, most recently a low-carbohydrate, high-fat diet. The patient's only other pertinent history is that she was told to watch her diet during pregnancy because of excessive weight gain. Her baby had to be delivered by cesarean because he weighed more than 9 lb. Her family history is not known, as she was adopted. On physical examination, her blood pressure is 138/88 mm Hg, her pulse is 72 beats/min, and her respiratory rate is 16 breaths/min. Her height is 65 in and her weight is 190 lb (body mass index [BMI] = 31.6). Her physical examination reveals darkened skin that appears to be thickened on the back of her neck and moist, reddened skin beneath her breasts. Her pelvic examination reveals a thick, white, vaginal discharge. A wet preparation from the vaginal discharge reveals branching hyphae consistent with *Candida*. A urine dipstick is performed that is negative for leukocyte esterase, nitrites, protein, and glucose.

- What is the most likely primary diagnosis for this patient?
- What physical findings does she have that are suggestive of the diagnosis and have implications for management?
- What diagnostic studies should be ordered at this time?

ANSWERS TO CASE 51:
Diabetes Mellitus

Summary: A 30-year-old obese woman presents with a difficult-to-treat yeast infection and polyuria. She has gained 40 lb in spite of efforts to lose weight. She has a history of significant weight gain and having been told to "watch her diet" during a pregnancy. On examination she is found to have a BMI of 31.6, acanthosis nigricans, candidal vaginitis, but a negative urine dip.

- **Most likely diagnosis:** Type 2 diabetes mellitus.
- **Significant physical findings:** Obesity, acanthosis nigricans, blood pressure that is elevated for a diabetic (goal is <135/85 mm Hg), candidal vaginitis, and possibly candidal skin infection under her breasts.
- **Diagnostic studies:** Blood glucose measurement (random sugar can be checked in the office with a fingerstick sample); follow-up testing should include electrolytes, blood urea nitrogen (BUN), creatinine, fasting lipids, urine microalbumin: creatinine ratio, and hemoglobin A_{1c}.

ANALYSIS

Objectives

1. Know the diagnostic criteria for diabetes mellitus, including, signs and symptoms, physical findings, and diagnostic studies.
2. Know the pathophysiologic and epidemiologic differences between type 1 and type 2 diabetes mellitus.
3. Learn the treatment options for diabetic patients.
4. Be aware of the acute emergencies that can occur to diabetics and how to manage them.

Considerations

Diabetes mellitus is one of the most common medical problems encountered in medical practice. There are an estimated 23.6 million (~8%) diabetics in the United States and the number is increasing both in the United States and worldwide. Diabetes affects all ethnic groups, but there is a disproportionate burden of disease in African Americans, Native Americans, and Hispanics. The global epidemic of obesity has led to a dramatic increase in the number of type 2 diabetics presenting with disease in their teens and twenties.

The complications of diabetes are myriad. Diabetics are 6 to 10 times more likely than nondiabetics to be hospitalized for cardiovascular disease and 15 times more likely to be hospitalized for peripheral vascular diseases.

It is the leading cause of blindness in working-age adults in the United States, most of which is preventable. It is also the leading cause for end-stage renal disease and nontraumatic amputations. In 2007, the direct and indirect cost related to diabetes mellitus was estimated to be $174 billion dollars.

Other complications that may be less well known to patients but that are attributable to diabetes include neuropathic, gastrointestinal, and immunologic changes. Peripheral neuropathy, leading to reduced sensation or pain, can lead to the development of ulcerations, infections, or injuries of the extremities. Gastroparesis can be a difficult-to-manage problem that makes diabetes more difficult to manage by impairing the patient's ability to eat properly. Immunologic changes make diabetics more prone to opportunistic infections, such as fungal skin or genitourinary infections.

Impaired glucose tolerance or frank diabetes may be present for years prior to the diagnosis of type 2 diabetes. In the case presented, the history of excessive weight gain during pregnancy with a large baby and cautions on watching her diet may be a sign of a history of gestational diabetes. Women with gestational diabetes have an increased risk of developing nongestational diabetes.

As in the case presented, difficult-to-treat or recurrent fungal infections may be the initial presentation that leads to the diagnosis of diabetes. This patient has both vaginal and skin infections. Although, in this case, the diagnosis is diabetes, other immune deficiency states must be considered when recurrent fungal infections are found. In the appropriate setting, HIV or other immunosuppressive conditions must be considered.

The symptom of polyuria should also lead to an increased suspicion for diabetes. High serum glucose levels function as an osmotic diuretic, resulting in frequent urination. This is often associated with polydipsia, a state of extreme thirst. Patients with type 1 diabetes also may present with polyphagia. Their lack of insulin prevents their food intake from being appropriately metabolized, resulting in a state of hunger for which they will frequently eat but not feel sated.

The absence of glucose in the urine dipstick does not exclude the diagnosis and should not delay a blood glucose measurement. Glucosuria occurs when the blood glucose level is greater than a renal "threshold" level, above which the glucose will spill into the urine. The lack of glucosuria only shows that the blood sugar level is not above this threshold level. Overt signs of insulin resistance (acanthosis nigricans, elevated blood pressure, obesity) also make the diagnosis of type 2 diabetes more likely.

General approach to managing diabetes is geared at secondary prevention of macrovascular (accelerated coronary artery disease, accelerated cerebral and peripheral vascular disease) and microvascular (retinopathy, nephropathy and neuropathy) complications. Overall diabetic patient should be "controlled": (1) glycemic control with a goal of hemoglobin A_{1c} of 6.5% or less, (2) LDL 70 to 100, (3) BP less than 130/80 mm Hg, and (4) life style modifications including a diet consisting of low carbohydrates and low saturated fat and physical activity counseling (at least 150 min/wk of moderate-intensity aerobic physical activity [50%-70% maximum heart rate] and resistance training [3 times/wk]).

APPROACH TO
Diabetes Mellitus

DEFINITIONS

DCCT: Diabetes Control and Complications Trial, a large, prospective, randomized controlled study of the advantages and disadvantages of "tight" versus "loose" diabetic control in type 1 diabetes.

UKPDS: United Kingdom Prospective Diabetes Study, a large, prospective, randomized controlled study of interventions and outcomes in type 2 diabetes.

CLINICAL APPROACH

Diabetes mellitus is a general term for several different diseases that result in high blood sugar levels and that eventually lead to microvascular and macrovascular complications. The major classifications of diabetes mellitus are type 1 diabetes, type 2 diabetes, and gestational diabetes.

Type 1 diabetes

Type 1 diabetes (previously called juvenile diabetes, juvenile-onset diabetes mellitus [JODM], or insulin-dependent diabetes mellitus [IDDM]) results from destruction of insulin-producing pancreatic β cells. The pathogenesis of type 1 diabetes mellitus is mediated by multiple risk factors that include viral infections, genetic susceptibility, and environmental risks.

Because of the lack of insulin, which is required for the metabolism of glucose, type 1 diabetics are prone to metabolize fats, with the resultant production of ketones. An extreme result of this process is **diabetic ketoacidosis,** a syndrome characterized by hyperglycemia, high levels of serum acetone, and an anion gap metabolic acidosis. This often occurs during times of physical stress, such as an infection or myocardial infarction, or when the patient does not use his or her insulin. Diabetic ketoacidosis is a medical emergency, requiring hospitalization, careful insulin management, correction of acidosis and electrolyte disturbances, and evaluation for the underlying cause of the condition.

Type 2 diabetes

Type 2 diabetes (previously called adult onset diabetes mellitus [AODM], non–insulin-dependent diabetes mellitus [NIDDM]) patients, in contrast to type 1 diabetics, in whom there is a lack of insulin, are typically hyperinsulinemic. Their disease results primarily from insulin resistance in the peripheral tissue and this resistance is often related to obesity. Type 2 diabetics often manifest signs of insulin resistance for many years prior to the diagnosis of

overt diabetes. This type accounts for at least 90% of the diagnosed cases, and virtually all undiagnosed diabetes, in the United States.

Type 2 diabetes has a stronger familial predisposition than type 1. Type 2 diabetics often have a family history of the disease. The genetic factors are multifactorial and have not been identified. It is strongly associated with obesity and its complications: metabolic syndrome, hyperinsulinemia, hypertension, dyslipidemia, hyperglycemia, and central obesity.

Uncontrolled type 2 diabetics can achieve extremely high blood sugars without developing ketosis and acidosis. This type is more prone to hyperosmolar states because of the high blood sugar levels. **Nonketotic hyperosmolar syndrome** occurs when blood sugar levels become highly elevated, often approaching 1000 mg/dL. This may be the presenting symptom of type 2 diabetes, or may result from a concurrent illness or failure to take medications. The serum osmolarity is elevated and the patient has a large fluid deficit. In severe cases, coma or death can occur. This can be managed with hospitalization, rehydration, treatment of underlying illnesses, and, sometimes, the judicious use of insulin to overcome the acute glucose toxicity.

Gestational diabetes

Gestational diabetes occurs in 3% to 10% of all pregnancies. Typically, women have 50% more insulin in their third trimester. Gestational diabetes is triggered by increased insulin resistance caused by elevated chorionic somatomammotropin, progesterone, and estrogens all of which act as insulin antagonist. Maternal and fetal complications are numerous. Maternal complications are hyperglycemia, DKA, increased UTI risk, increased pregnancy induced hypertension/preeclampsia, and retinopathy. Fetal effects are congenital malformations, macrosomia, respiratory distress syndrome, hypoglycemia, hyperbilirubinemia, hypocalcemia, polycythemia, and hydramnios. Women with gestational diabetes are more prone to develop non–pregnancy-related type 2 diabetes and should be screened with a glucose tolerance test postpartum.

Risk factors for gestational diabetes include age older than 25 years, member of a high-incidence racial group (Native American, African American, Hispanic American, South or East Asian, Pacific Islander), body mass index of 25 or more, history of glucose intolerance, previous history of gestational diabetes, and history of diabetes in a first-degree family member.

The American College of Obstetricians and Gynecologists recommends screening all women for gestational diabetes. A 50-g 1-hour glucose challenge test (GCT) is administered to all pregnant women at 26 to 28 weeks, followed by a 100-g, 3-hour oral glucose tolerance test (OGTT) for those with an abnormal screening result. If 1-hour glucose challenge is greater than 140 then 100-g 3-hour glucose challenge is needed. Diagnosis is made based on greater than two abnormal results. Gestational diabetes is treated with careful diet management via patient education and nutritional counseling and when necessary, insulin.

DIAGNOSIS

The diagnostic criteria for diabetes are:

1. A random glucose 200 mg/dL or more along with classic symptoms that include polydipsia, polyuria, polyphagia, frequent infections, and weight loss
2. A fasting glucose more than 125 mg/dL on at least two occasions
3. A 2-hour plasma glucose 200 mg/dL or more after a 75-g glucose load

Glycosylated hemoglobin or hemoglobin A_{1c} (HbA_{1c}) is not recommended for diagnosis. This test is used to estimate the average glucose over the past 3 months in those who are diagnosed with diabetes. Measurement of C-peptide and insulin levels can be used to distinguish type 2 from type 1 diabetes when the history, physical examination, and other tests, such as serum ketones and osmolality, are not enough. Other tests recommended by the American Diabetes Association are fasting lipid profiles (at the time of diagnosis and, at least, annually thereafter), serum creatinine, urinalysis, urine microalbumin:creatinine ratios (at time of diagnosis in type 2 diabetics and annually thereafter; in type 1 diabetics who have had disease for 5 years and annually thereafter), annual dilated eye examinations, regular foot examinations, ECG (in adults), and, in type 1 diabetics, thyroid disease screening with a thyroid-stimulating hormone (TSH).

MANAGEMENT

The **treatment for type 1 diabetes involves the use of insulin.** In most cases, combination therapy using short-acting insulin prior to meals and an intermediate- or long-acting basal insulin is used. Insulin pump therapy, which provides a continuous subcutaneous infusion of short-acting insulin, is an alternative. Insulin management requires careful and frequent self-monitoring of glucose, often with adjustment of insulin dosage based on the glucose levels, amount of physical activity, and caloric/carbohydrate intake (see Table 51-1).

Type 2 diabetics and those at risk of developing diabetes should be educated on the importance of diet and exercise as key components of their management. In some cases, that will be all that is needed to achieve appropriate control. An initial goal that is achievable by many is a 10% weight loss. When lifestyle changes alone do not result in adequate control, numerous oral agents are available. For severely obese patients, surgical gastric bypass may be considered, although long-term risk and benefits have not been fully explored.

Medications for prevention are currently not recommended but can be considered if lifestyle modification is unsuccessful. Several mediations are available for treating type 2 diabetes (Table 51–2). Metformin is the drug of choice to begin with unless contraindications are present.

Biguanides (metformin) act on the liver to **decrease glucose output during gluconeogenesis.** Secondary actions include improved insulin sensitivity in the liver and muscle and a hypothesized decrease in intestinal absorption

Table 51–1 INSULIN PREPARATIONS

TYPE OF INSULIN	ONSET OF ACTION	PEAK OF ACTION	DURATION OF ACTION
Rapid acting (lispro or aspart insulin)	15 min	30-90 min	3-5 h
Short acting (regular insulin)	30-60 min	60-120 min	5-8 h
Intermediate acting (neural protamine hagedorn [NPH] insulin)	13 h	7-15 h	18-24 h
Long acting (glargine insulin; insulin detemir)	1 h	None	24 h

Data from the National Institutes of Health, available at: http://diabetes.niddk. nih.gov/dm/pubs/medicines_ez/insert_C.htm. Accessed May, 2009.

of glucose. Metformin can lower the HbA_{1c} by 1.5% to 2%. The UKPDS showed a significant reduction in cardiovascular events, diabetes-related deaths, and all causes of mortality in those who used metformin. Other advantages include no potential hypoglycemia, reduced insulin levels, a potential weight loss, and a reduction in triglycerides and low-density lipoprotein (LDL) cholesterol. The efficacy, safety, and improved outcomes make it a popular first-line agent in type 2 diabetes

The most common side effects are gastrointestinal, such as nausea and diarrhea. These side effects are reduced by starting with lower doses and giving the medication with meals. The more dangerous side effect is the development of lactic acidosis. The risk of this potentially fatal side effect is increased by renal insufficiency. Metformin use is contraindicated in those with a creatinine more than 1.5 mg/dL in men and more than 1.4 mg/dL in women, hepatic insufficiency, or congestive heart failure. It is Category B in pregnancy and probably safe in nursing mothers. It is the oral agent of choice in type 2 diabetes in children older than age 10 years.

Sulfonylureas were the first oral agents available for type 2 diabetes. Their principal action is to function as **insulin secretagogues** that stimulate β cells in the pancreas to secrete insulin. Advantages include a potential 2% reduction in HbA_{1c}, once- or twice-a-day dosing, and relatively low cost. Disadvantages are poor response in 20% of patients, a tendency of the users to gain weight, and a tendency for the medications to lose effectiveness over time. As insulin secretagogues, sulfonylureas carry a risk of causing hypoglycemia.

Table 51–2 ORAL HYPERGLYCEMICS

INTERVENTION	% DECREASE IN HBA_{1C}	ADVANTAGES	DISADVANTAGES
Tier 1: well-validated core **Step 1:** initial therapy Lifestyle: to decrease weight and increase activity	1.0-2.0	Broad benefits	Insufficient for most within first year
Metformin	1.0-2.0	Weight neutral	GI side effects, contraindicated with renal insufficiency
Step 2: additional therapy Insulin	1.5-3.5	No dose limit, rapidly effective, improved lipid profile	One to four injections daily, monitoring, weight gain, hypoglycemia, analogues are expensive
Sulfonylurea	1.0-2.0	Rapidly effective	Weight gain, hypoglycemia (especially with glibenclamide or chlorpropamide)
Tier 2: less well validated TZDs	0.5-1.4	Improved lipid profile (pioglitazone), potential decrease in MI (pioglitazone)	Fluid retention, CHF, weight gain, bone fractures, expensive, potential increase in MI (rosiglitazone)
GLP-1 agonist	0.5-1.0	Weight loss	Two injections daily, frequent GI side effects, long-term safety not established, expensive

Table 51–2 ORAL HYPERGLYCEMICS (CONTINUED)

INTERVENTION	% DECREASE IN HBA_{1C}	ADVANTAGES	DISADVANTAGES
Other therapy: Glucosidase inhibitor	0.5-0.8	Weight neutral	Frequent GI side effects, tid dosing, expensive
Glinide	0.5-1.5	Rapidly effective	Weight gain, tid dosing, hypoglycemia, expensive
Pramlintide	0.5-1.0	Weight loss	Three injections daily, frequent GI side effects, long-term safety not established, expensive
DPP-4 inhibitor	0.5-0.8	Weight neutral	Long-term safety not established, expensive

Data from: Nathan DM, Buse JB, Davidson MB, et al. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm of initiation and adjustment of therapy. Diabetic Care. *2008;31(12):1-11.*

Sulfonylureas and insulin are considered the best validated second-line add-on therapy. The following medications are less well validated. Further studies are necessary to determine how these agents may play a role in the overall care of type 2 diabetics.

The principal action of **thiazolidinediones** (TZDs) is **improving insulin sensitivity in muscle and adipose tissue.** Secondary actions are decreased hepatic gluconeogenesis and increased peripheral glucose utilization. Among their advantages is a decrease in triglyceride and increase in high-density lipoprotein (HDL) cholesterol levels. Because they are metabolized in the liver, they can be used in patients with renal impairment. They also do not, when used by themselves, cause hypoglycemia. Disadvantages include a slight increase in LDL cholesterol, weight gain, and a slow onset of action. These agents may take up to 12 weeks to fully become effective. They cause water

retention, which is of concern with renal compromise and congestive heart failure. There is some current controversy on whether the benefits of this class of medications outweigh the risks.

Meglitinides are **short-acting secretagogues** that increase insulin secretion from the pancreas. These medications are taken no more than 1 hour before meals because of the rapid onset and short duration of action. They are useful in patients whose blood sugars vary at mealtime but who have controlled fasting glucose levels. They reduce HbA_{1c} levels from 0.5% to 2%. The disadvantages include a risk of hypoglycemia (especially if the medication is taken but no meal is then eaten) and expense. They should not be used in patients with hepatic dysfunction.

α-Glucosidase inhibitors delay carbohydrate absorption by inhibiting α-glucosidase in the small intestine, which decreases postprandial hyperglycemia. They reduce HbA_{1c} levels by 0.7% to 1.0%. This class of medication may offer benefits to patients with erratic eating habits, as hypoglycemia will not occur if meals are skipped. The principal side effects are GI, including flatulence. These medications are contraindicated in ketoacidosis and in hepatic disorders.

Pramlintide is an amylinomimetic agent that has physiologic actions equivalent to those of human amylin (glucoregulatory hormone synthesized by pancreatic β cells and released with insulin in response to a meal). It inhibits inappropriately high glucagon secretion during episodes of hyperglycemia (eg, after a meal) in patients with type 1 or type 2 diabetes mellitus and does not impair normal glucagon response to hypoglycemia. It is a subcutaneous medication that does not require adjustments for renal or hepatic impairment. It reduces HbA_{1c} levels by 0.5% to 1.0%. Known side effects are hypoglycemia and nausea and diarrhea. Often dosing requires titration to balance hypoglycemia and preprandial glycemic control.

GLP-1 Agonist (glucagon-like peptide-1 mimetic). Exenatide (Byetta) is an incretin mimetic which belongs to this class. It is a synthetic peptide that stimulates insulin release. Adjunctive therapy for type 2 diabetics with inadequate glycemic control while on either metformin, sulfonylurea, and/or thiazolidinedione (glitazone). It reduces HbA_{1c} levels by 0.5% to 1.0%. Side effects include hypoglycemia when added to sulfonylurea (but not when added to metformin), nausea, vomiting, diarrhea, and acute pancreatitis.

DPP-4 Inhibitor (dipeptidyl peptidase-4 inhibitor). Sitagliptin (Januvia) inhibits dipeptidyl peptidase-4 (DPP-4), an enzyme that inactivates incretin hormones glucagon-like peptide (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). GIP and GLP-1 stimulate insulin synthesis and release from pancreatic β cells in a glucose-dependent manner. GLP-1 also decreases glucagon secretion from pancreatic α cells in a glucose-dependent manner, leading to reduced hepatic glucose production. Used as monotherapy and as an adjunct to diet and exercise for management of type 2 diabetes mellitus in patients whose hyperglycemia cannot be controlled by diet and exercise alone. Used in combination with metformin, a sulfonylurea, or a thiazolidinedione as

second-line therapy for management of type 2 diabetes mellitus in patients who do not achieve adequate glycemic control with diet, exercise, and metformin, sulfonylurea, or thiazolidinedione monotherapy. It reduces HbA_{1c} levels by 0.5% to 0.8%. The principal side effects are upper respiratory symptoms and severe hypersensitivity (ie, anaphylaxis and/or angioedema).

The goal of diabetic management is to safely lower the blood sugar so as to reduce the risk of macrovascular and microvascular complications. Both the UKPDS and DCCT showed lower rates of complications in controlled diabetes. The goal of treatment is to achieve a HbA_{1c} of less than 7%, although some authorities are now advocating 6.5% as a goal. Goal fasting blood sugar is less than 120 mg/dL and 2-hour postprandial sugar is less than 140 mg/dL.

Other treatments are equally important to tight glucose control in the effort to reduce adverse events, such as heart attacks and strokes. The UKPDS clearly showed that tight blood pressure control is effective in reducing cardiovascular events. The blood pressure goal in diabetes is less than 135/85 mm Hg. Diabetes is considered a coronary heart disease risk equivalent for decisions regarding lipid management. The goal LDL cholesterol level is less than 100 mg/dL. All diabetics should be advised to be immunized with the pneumococcal vaccine and to get annual influenza vaccination.

MANAGEMENT OF HYPOGLYCEMIA

Hypoglycemic symptoms are related to the brain and the sympathetic nervous system. Decreased levels of glucose lead to deficient cerebral glucose availability that can manifest as confusion, difficulty with concentration, irritability, hallucinations, focal impairments (eg, hemiplegia), and eventually, coma and death. Stimulation of the sympatho-adrenal nervous system leads to sweating, palpitations, tremulousness, anxiety, and hunger.

Causes of hypoglycemia include fasting, exogenous insulin, autoimmunity, sulfonylurea abuse, hormonal deficiency (hypoadrenalism, hypopituitary, glucagon deficiency).

When hypoglycemia is suspected and the patient is conscious and cooperative, juice, soda, candy, or some other sugar-containing product can rapidly alleviate the symptoms. If the person is not able to take something by mouth, rapid administration of IM glucagon can be effective. In a hospital setting, or when IV access is available, an injection of 50% dextrose (D_{50}) rapidly corrects the problem. Following any of these therapies, the patient should be closely watched, as the hypoglycemia may recur (especially if the patient uses a long-acting insulin or oral hypoglycemic agent).

Comprehension Questions

51.1 A 16-year-old adolescent female has had an increased craving for sweets. She often consumes two to three ice cream sundaes and four large sodas a day but has still managed to maintain her weight. Friends often notice her using the bathroom more frequently but she denies any episodes of purging and states that she just has to urinate after drinking so much cola. On physical examination she is 5 in 8 ft and 110 lb and thyroid is nonpalpable. Which of the following test results is diagnostic of diabetes mellitus?

A. Single fasting glucose of 150 mg/dL
B. A 2-hour oral glucose tolerance test greater than 200 mg/dL with a 100-g glucose load
C. A random glucose greater than 200 mg/dL with symptoms such as polydipsia or polyuria
D. A HbA_{1c} greater than 7.5%

51.2 A 7-year-old is brought to the office with symptoms of polydipsia, polyphagia, polyuria, and weight loss of 8 lb. For the past 24 hours he has had abdominal pain and vomiting. An urinalysis done in the office shows the presence of glucose and ketones. A fingerstick blood glucose is more than 500 mg/dL. Which of the following is the most appropriate management?

A. Prescription for oral metformin and referral to a nutritionist
B. Hospitalization with institution of insulin and IV fluids
C. Prescription for insulin to be started at home, with follow-up in 24 hours
D. Treatment for acute gastroenteritis and referral to an endocrinologist

51.3 A 83-year-old man who was diagnosed with type 2 diabetes 3 months ago. He has altered his diet and tries to walk at least half a mile in the evenings. He drinks a glass of wine with lunch and dinner. For the past week he has felt dizzy upon standing and has fallen on two occasions but he never lost consciousness. After the last episode he presented to the local ER where his blood pressure was found to be 155/76 mm Hg, HR 74 beats/min, and RR 16 breaths/min. A finger stick showed a glucose level of 84. Which of the following classes of medications has the lowest incidence of causing hypoglycemia when given as single-agent therapy?

A. Biguanide
B. Insulin
C. Sulfonylurea
D. Meglitinide

51.4 A 38-year-old G1P0 woman who is a new patient presents to the office at 10-week gestation. She is known to have type 2 diabetes. She currently takes metformin and her last HbA_{1c} was 10.4%. Her urine dip is negative for ketones, protein, and leukocytes. She has no other medical problems and does not drink or smoke. On physical examination she is 5 in 4 ft and weighs 202 lb. She inquires about the risk to her fetus. As compared to gestational diabetes, this patient is at increased risk for which of the following?

A. Fetal malformations
B. Fetal macrosomia
C. Polyhydramnios
D. Shoulder dystocia

ANSWERS

51.1 **C.** Diabetes mellitus can be defined by two separate measurements of a fasting glucose more than 125 mg/dL; a random glucose of 200 mg/dL or more with classic symptoms or a 2-hour glucose tolerance test of 200 mg/dL or more after a 75-g glucose load. HbA_{1c} should not be used in diagnosing diabetes.

51.2 **B.** This is a typical presentation of diabetic ketoacidosis, a medical emergency. This is a common initial presentation of type 1 diabetes. This child requires immediate hospitalization, IV fluids, and insulin.

51.3 **A.** Biguanides (metformin) are effective medications for the treatment of type 2 diabetes; they do not cause hypoglycemia when given as monotherapy. Insulin and insulin secretagogues carry a risk of hypoglycemia as a complication of therapy.

51.4 **A.** Gestational diabetes is more likely to lead to fetal macrosomia and polyhydramnios. Both gestational and pregestational diabetes are associated with shoulder dystocia. Pregestational diabetes is associated with greater fetal malformations due to the higher serum glucose levels during organogenesis (5-10 weeks gestational age), whereas gestational diabetes tends to be associated with hyperglycemia after 20 weeks gestation, when the fetal organs have already formed. Preterm labor occurs at same frequency in diabetics as nondiabetics.

Clinical Pearls

- Diabetes is one of the most common diseases in clinical practice. The criteria for diagnosis have been lowered to decrease complications, including death.
- Type 2 diabetes accounts for more than 90% of all diabetes in the United States. The increasing presence of obesity is, unfortunately, driving the incidence of type 2 diabetes even higher.
- Biguanides are gaining favor in the treatment of type 2 diabetes because of their potency and demonstrated reduction in morbidity and mortality.

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Case 52

A 74-year-old African-American woman enters your office with the complaint that she has been developing bruises all over her extremities for the last several days. She also has noticed that her stool seems to be a lot darker. She describes it looking almost like coffee grounds. She relocated to your area to live with her daughter after her home in Galveston was destroyed several months ago. This is her initial visit to your office, as she had refills available for all of her medications and previously felt fine. Her past medical history is notable for being hypertensive, postmenopausal, having an irregular heartbeat that she doesn't remember the exact name for, and having a touch of diabetes and arthritis. Her prescribed medications are hydrochlorothiazide and warfarin. Her over-the-counter medications include aspirin which she started taking since moving to your city, a multivitamin, acetaminophen for her arthritis and ibuprofen for when her knees really bother her. She also admits to regularly drinking herbal teas.

- What is the differential diagnosis for this patient's presentation?
- What diagnostic studies are indicated?
- Why are the elderly at increased risk for the development of adverse drug reactions?

ANSWERS TO CASE 52:
Adverse Drug Reactions and Interactions

Summary: A 74-year-old woman presents with easy bruising and dark stools for several days. She is new to your practice, but is on an antihypertensive medication and a blood thinner. She is also taking numerous over-the-counter medications.

- **Differential diagnosis:** Includes an adverse drug interaction involving her warfarin and the aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen that she is currently taking. Other (much less likely) possibilities include bleeding from a gastrointestinal malignancy, liver disease, or hematologic abnormality (acute leukemia or severe thrombocytopenia).
- **Necessary diagnostic studies:** This patient should have a test for stool occult blood in the office, a stat complete blood count (CBC), a prothrombin time (PT) with international normalized ratio (INR), a metabolic panel, and an ECG. It would be appropriate to consider this patient for observation status in the hospital while her studies are pending.
- **Reasons for increased risk of drug reactions in the elderly:** Numerous issues, including polypharmacy, changes in renal and hepatic function, and pharmacodynamic considerations (change in body composition and volume of distribution) that develop with aging.

ANALYSIS

Objectives

1. Understand the scope and risk of the problem of drug interactions and adverse effects.
2. Learn some mechanisms to reduce these risks.
3. Know why the elderly are particularly vulnerable to potential complications.

Considerations

The extensive use of medications—including prescribed, over-the-counter, herbal, and homeopathic products—makes adverse drug reactions and interactions a significant public health concern. About one in three older persons taking at least five medications will experience an adverse drug event each year and about two-thirds of these patients will require medical attention. A Harvard study revealed that **6.5% of hospital inpatients experienced a documented injury secondary to medications.** Because of physiologic changes and the use of multiple medications for multiple medical conditions, the elderly

are at increased risk. **An estimated 3% to 11% of hospital admissions in the elderly are related to adverse drug reactions.**

The patient presented has numerous risks for the development of serious problems related to her medications. As noted before, her age alone is a risk. The use of warfarin is another, as its use should be closely monitored. Having been on this medication while not under the care of a physician, after leaving Galveston and prior to establishing care, is a danger in itself. Warfarin also has numerous drug-drug interactions, among them are an increased risk of bleeding with the concomitant use of aspirin, NSAIDs, or acetaminophen.

Because of her age, the presence of bruising (suggesting an increased PT from her medications), and the possibility of rectal bleeding, she should have a fecal occult blood test (FOBT) done and she should be screened for anemia with a CBC. She should also have a PT with INR to evaluate her degree of anticoagulation and risk for ongoing hemorrhage. Because of her age and comorbid conditions, she should also have a metabolic panel to evaluate her glucose, electrolytes, and renal and liver functions, and an ECG to evaluate for signs of ischemia. With the possibility of significant abnormalities on these tests that may require urgent management, it would be reasonable to place her in observation status in the hospital for monitoring and treatment. Eventually, although probably not necessary in the acute setting, she would require a colonoscopy to ensure that there is not an underlying colorectal cancer contributing to her bleeding.

If she is found to have a prolonged PT, several therapeutic options are available, depending on the clinical situation and the magnitude of the abnormality. For mildly over-anticoagulated patients with no evidence of bleeding, temporary discontinuation of warfarin or dose reduction is often all that is needed. For more prolonged prothrombin times, vitamin K orally along with stopping the warfarin, can correct most abnormalities within a few days. When the PT is very high, or if there is evidence of bleeding, intravenous vitamin K and replacement of coagulation factors with a transfusion of fresh-frozen plasma will rapidly reverse the coagulopathy.

APPROACH TO
Adverse Drug Reactions and Interactions

DEFINITION

CYTOCHROME P450 (CYP): An enzyme system found mostly in the liver (but also in the small intestine, lungs, and kidneys) that is composed of more than 50 isoenzymes, and which is responsible for the metabolism of numerous medications. The **CYP isoenzymes can be induced,** resulting in increased drug metabolism and reduced therapeutic benefit of a medication, **or blocked,** resulting in decreased drug metabolism and potential for drug toxicity.

CLINICAL APPROACH

Etiologies of Adverse Drug Effects

Side effects are defined as effects from drugs that are beyond their intended therapeutic scope. These effects may be either adverse or beneficial. Adverse side effects can range from minor nuisances, such as nausea or diarrhea, to severe or life-threatening, such as cardiac arrhythmias precipitated by antiarrhythmic or stimulant medications. Other side effects have been found that are beneficial. For example, peripheral α-adrenergic blockers, initially used as antihypertensives, were found to alleviate obstructive symptoms from prostatic hyperplasia and are now widely used for this purpose. Another example is minoxidil, also an antihypertensive agent, which was found by some users to result in hair growth, so it is now marketed as treatment for hair loss.

Drug interactions account for 5% to 10% of adverse reactions. Drug interactions may be caused by pharmacokinetic effects, resulting in a change in either the drug's concentration or the drug's effect. Some of these interactions may be predictable, as a consequence of chemical effects secondary to enzymatic effects, protein binding, renal and hepatic interactions, and pharmacodynamic interactions. Warfarin may interact with several other medications and dietary factors to increase the active form of this drug to toxic levels, resulting in over-anticoagulation with resultant bruising and hemorrhage.

Drugs also may have additive effects caused by using two or more agents designed to produce a similar outcome working synergistically. An example of this is using a β-adrenergic blocking agent with certain calcium channel blockers (diltiazem, verapamil). Both medications can decrease heart rate but by different mechanisms of action. Combining the two may result in profound bradycardia and hypotension.

Other **interactions may be more directly related to the chemical characteristics** of the medications or the solutions in which they are delivered. For example, mixing glargine insulin with other insulin types in the same syringe may result in precipitation of the insulin product, rendering them ineffective. Similarly, some IV medications must be administered individually while others can be combined.

To avoid misuse of medications in the elderly, and to identify high risk medications, an expert consensus panel has met regularly to develop the most widely used list of medications that should be avoided. This list is called the **Beers criteria.** Many of these medications are sedating or have anticholinergic effects that increase the risk of falls. Others have narrow therapeutic indexes, increasing the risk of toxic serum levels developing. There are often equally effective alternatives available. If a patient is already on these medications, lowering the dose to the minimum effective dose is another way of minimizing risk. The full list of medications is available at http://archinte.ama-assn.org/cgi/content/full/163/22/2716.

Drug Metabolism

Many drugs are metabolized in the liver. **Medications with a high first-pass hepatic clearance may be particularly susceptible to adverse events caused by alterations in hepatic metabolism.** Diseases that change the effective circulatory volume, such as congestive heart failure, may also alter the rate of drug or metabolite elimination because of the effects on hepatic and renal blood flow.

The CYP system plays a significant role in many real or potential adverse drug events. Although more than 50 CYP isoenzymes have been identified, 6 of these isoenzymes metabolize 90% of drugs.

Alcohol has effects on the 2E1 isoenzyme. This isoenzyme can produce a hepatotoxic metabolite of acetaminophen. Because of this, the chronic use of alcohol and acetaminophen can induce liver damage, and an acetaminophen overdose, which is already potentially toxic to the liver, is made worse if mixed with alcohol.

Drugs that have a significant first-pass effect may have an effect on metabolism in the liver or absorption in the intestine. For example, increased levels of the 3A isoenzyme may result in alterations in the level, and therefore therapeutic effect, of cyclosporine.

Many drugs are albumin bound. When multiple agents are competing for the same albumin binding sites, there is a potential to have greater amounts of unbound medication, resulting in higher circulating free drug levels. This causes particular concern for drugs that have a smaller volume of distribution, rapid onset of action, or narrow therapeutic index.

Renal considerations are related to interaction of drugs at renal sites and decreased renal function. Renal interactions are often a result of alterations in the elimination of water-soluble drugs because of competition for the renal tubular system. These effects may be either positive or negative. An example of the beneficial effect of this is the concomitant administration of probenecid with penicillin. Probenecid decreases renal excretion of penicillin, resulting in an increased level and therapeutic effect of the antibiotic.

Other renal considerations include decreased kidney function secondary to either disease processes, such as hypertension or diabetes, or from the natural decline in renal function that occurs with aging. Many medications have recommendations for alteration in dosing amount or interval based upon the patient's creatinine clearance. Creatinine is a product of muscle and the elderly may have falsely elevated calculated creatinine clearance rates because they have decreased muscle mass. Creatinine clearance can be estimated using the following equation:

$$\text{Creatinine clearance} = \frac{[(140 - \text{age}) \times (\text{ideal body weight in kg})] \times (0.85 \text{ for women})}{72 \times \text{serum creatinine (mg/dL)}}$$

Interventions to Reduce the Risk of Adverse Drug Events

There are many possible interventions to reduce the risk of adverse drug events or interactions, especially in the older population, including the following:

- Use Beers Criteria when considering medications in the elderly. Only prescribe those medications that are clearly indicated. However, do not avoid a necessary medication.
- When someone presents with a new complaint consider adverse drug reaction (ADR) in the differential.
- Obtain a history of adverse events related to medications on all patients.
- Maintain a list of all medications that a patient is taking, including prescribed, over-the-counter, herbal, and homeopathic. Update this list at every visit.
- Instruct your patients to bring in **all** of their medications regularly to make sure your medication list is accurate.
- Routinely perform drug interaction surveys on patients taking multiple medications. Consider working with pharmacists (often available in nursing home settings) and using computerized tools available to perform these surveys, including several personal digital assistant (PDA)-based products.
- Have knowledge of renal, hepatic, and circulatory issues that affect your patients.
- Consider issues related to individual patients, such as unique genetic or racial factors.
- Document and report suspected adverse drug effects.

Comprehension Questions

52.1 A 62-year-old man with hypertension, hypercholesterolemia, and benign prostatic hypertrophy (BPH) presents to his physician with increasing muscle aches in his thighs and shoulders and complains of dark, tea-colored urine. These symptoms started about 10 days ago. He has been drinking plenty of fluids especially grapefruit juice as part of a new diet. On routine lab work his liver enzymes are profoundly elevated and his urine has significant amounts of protein in it. His only medicines are lisinopril, simvastatin, and a baby aspirin. Which of the following is the most likely diagnosis?

A. Drug-induced hepatitis from long-term simvastatin
B. BPH causing obstructive kidney damage and proteinuria
C. Renal failure secondary to combined aspirin and ACE inhibitor
D. Hepatic enzyme inhibition leading to elevated circulating drug levels

52.2 An 87-year-old man has diabetes, coronary heart disease, chronic renal insufficiency, and chronic obstructive pulmonary disease (COPD). He has newly diagnosed atrial fibrillation and needs to be anticoagulated. His current medications include metformin, glipizide, losartan, metoprolol, and ipratropium. Being aware of which of the following in the elderly is the most important consideration in avoiding adverse drug reactions?

A. Increased glomerular filtration rate
B. Polypharmacy
C. Inability to open medicine containers
D. Increased hepatic blood flow

52.3 A 36-year-old woman presents very distressed in your office after having a positive pregnancy test. She says that she has taken her OCP religiously at the same time every day for the past year. She is very healthy and has no significant past medical history except for mild depression. She says the only medicine she takes is a prescribed OCP besides her usual vitamins and herbal supplements. Which of the following additional information would be most helpful in discovering why her OCP may have failed?

A. Which OCP she is taking
B. Which particular herbal supplements she is taking
C. Her number of sexual partners
D. If she has ever been pregnant before

ANSWERS

52.1 **D.** Grapefruit juice inhibits cytochrome P450 enzymes that metabolize simvastatin. This patient probably has rhabdomyolysis from increased circulating simvastatin.

52.2 **B.** A multitude of factors result in the elderly being particularly vulnerable to adverse drug events. Included among these are polypharmacy, decreased renal and hepatic function, and pharmacokinetic and pharmacodynamic considerations.

52.3 **B.** Asking which herbal supplements can be very helpful. St. John's wort, a common herbal antidepressant, can induce CYP3A4 and 5 causing increased metabolism of estradiol.

Clinical Pearls

➤ Along with the biochemical changes that occur with aging, several physical conditions may also affect medication compliance. Arthritic patients may have difficulty opening prescription caps (especially childproof caps). Reduced vision may interfere with the ability to properly use a medication. Memory difficulties may cause trouble adhering to regimens involving multiple medications. All of these factors, and many others, need to be considered when prescribing medications to the elderly.

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Case 53

A previously healthy 48-year-old accountant presents to his primary care office for severe back pain. The pain started the previous day after he helped his daughter move into her college dorm. He denies any trauma. The pain is generally "achy," but sometimes characterized as "sharp" when he moves suddenly. It is located in his lower back and radiates down the back of both legs to his mid-hamstring. He has been continent of both bowel and bladder and denies any weakness in his legs. He denies fever, chills, weight loss, or malaise. It is very difficult to stand for long periods because he has a hard time finding a comfortable position. He has never had pain this bad in his back and has tried acetaminophen without much effect. He has no history of cancer or drug abuse. He is only on an antihypertensive and a baby aspirin per day. On examination, the patient was found to be well-developed, overweight, and in moderate discomfort. He had noticeable tenderness bilaterally in his lumbar paraspinous muscles, back range-of-motion limited by pain, and both negative straight leg raise and crossed straight raise tests. His lower extremities had normal strength, reflexes, and sensation.

- What is the most likely diagnosis?
- What is the most appropriate workup?
- What is the best treatment plan?

ANSWERS TO CASE 53:
Acute Low Back Pain

Summary: A previously healthy 48-year-old man presents with acute onset of low back pain after strenuous activity. His neurological examination is normal and he denies any systemic complaints.

- **Most likely diagnosis:** Acute low back pain also known as lower back strain
- **Workup:** Nothing more needed until after conservative treatment for at least 1 month
- **Treatment:** Rest, NSAIDs, and muscle relaxants

ANALYSIS

Objectives

1. Develop a differential diagnosis for low back pain and explore it with the history and physical.
2. Learn the "red flag" symptoms of low back pain and how to follow them up.
3. Learn the effective treatments for musculoskeletal back pain.

Considerations

Acute low back is the fifth most likely reason for a visit to the doctor. Unfortunately, approximately 85% of patients who present with isolated low back pain will never be given a specific anatomical reason for the pain. However, up to 90% of patients will recover within 2 weeks of diagnosis.

Since the initial differential of low back pain is broad, the job of the clinician is to decide whether the pain is caused by a systemic disease, if it is associated with a neurologic compromise, and to consider sociologic factors that may complicate the recovery or efficacy of treatment.

This patient's history includes pertinent positives of being overweight and a recent history of lifting and twisting that are associated with lumbar strain. His symptoms and examination are consistent with a localized musculoskeletal problem. His age and lack of systemic symptoms are pertinent negatives. He is not depressed or has a history of substance abuse. This clinical scenario is best managed by symptomatic therapies, without imaging, with close follow-up in 1 month. Education in lifting and exercise therapy may also be of special benefit to him.

APPROACH TO
Low Back Pain

DEFINITIONS

HERNIATED DISC: Rupture of the fibrocartilage between the vertebrae leading to leakage of the nucleus pulposus that may impinge on the nerve roots causing pain.

SCIATICA: Pain along the path of the sciatic nerve usually caused by a herniated disk of the lumbar region of the spine, which typically will radiate to the buttocks and to the back of the thigh.

CLINICAL APPROACH

Acute low back pain should be evaluated in a systematic manner to avoid missing important red flag symptoms (see Table 53-1) and unnecessary imaging, treatments, or referrals. The first step is to generate a differential diagnosis (see Table 53-2) and understand the common signs and symptoms of its components.

History, Physical, and Evaluation

The history triages more serious back problems into those needing urgent attention and those that can be worked up more methodically. Patients presenting with **cauda equina syndrome** have increasing neurological deficits and leg weakness, bowel and urinary incontinence, sensory loss in a saddle

Table 53–1 RED FLAG SYMPTOMS IN LOW BACK PAIN

Unrelenting night pain
Unrelenting pain at rest
Neuromotor deficit
Fever
Loss of bowel or bladder control
Suspicion of ankylosing spondylitis
Trauma
History or suspicion of cancer
Osteoporosis
Chronic corticosteroid use
Immunosuppression
Drug or alcohol abuse

Table 53–2 DIFFERENTIAL DIAGNOSIS OF LOW BACK PAIN

Condition (prevalence)
Mechanical low back pain (approx 97%)
• Lumbar strain, sprain (70%)
• Degenerative facets or disks (10%)
• Herniated disk (4%)
• Compression fracture (4%)
• Spinal stenosis (3%)
• Spondylolisthesis (2%)
• Spondylolysis (<1%)
Nonmechanical spinal conditions (1%)
• Cancer (primary or metastatic) (0.7%)
• Inflammatory arthritis (0.3%)
• Infection (0.01%)
Visceral disease (2%)
• Pelvic organs: prostatitis, PID, endometriosis
• Renal disease: nephrolithiasis, pyelonephritis, perinephric abscess
• Aortic aneurysm
• Gastrointestinal disease: pancreatitis, cholecystitis, peptic ulcer
• Shingles

Data from Kinkade, S. Evaluation and treatment of acute low back pain. Am Fam Physician. *2008;75:1181-1188, 1190-1192; and Deyo RA, Weinstein JN. Low back pain.* N Engl J Med. *2001;344(5): 363-370.*

distribution, and bilateral sciatica. These patients need immediate evaluation with lumbar MRI, surgical decompression of the entrapped cauda equina, and probable operative management. Fevers, direct vertebral tenderness, recent infections, and a history of intravenous drug use can point toward an **infectious** process like osteomyelitis, septic diskitis, paraspinous abscess, or epidural abscess. These infections are evaluated by CBC, ESR, and MRI and require long courses of intravenous antibiotics and sometimes surgical drainage. An underlying **cancer** is much more likely if the patient has a history of cancer (up to 9% chance), unexplained weight loss, failure to improve after 1 month of therapy, or an age greater than 50 years old. To further evaluate people with these risk factors a CBC, ESR, and plain radiographs should be gotten initially. Abnormalities in these tests should be further evaluated by MRI and/or a bone scan. Common cancers that involve the spine include multiple myeloma and metastatic prostate, breast, and lung.

The history also helps differentiate less urgent but important causes of back pain. Sciatica is the classic sign of a **herniated disc**. It is a back pain that radiates distal to the knee. It increases with Valsalva, sneezing, or coughing. It can be examined by doing both a straight-leg-raise (91% sensitive, 26% specific)

and a contralateral leg raise test (29% sensitive, 88% specific), along with sensory, strength, and reflex testing of the lower extremities (L4-knee strength and reflex, L5-great toe and foot dorsiflexion, and S1- plantaflexion and ankle reflexes). Greater than 90% of lumbar disc compression of nerve roots occurs at L4/L5 and L5/S1. MRI is not recommended for patients with sciatica unless the symptoms last for greater than 1 month or if the patient is not a candidate for surgery or epidural injection. Conservative treatment involves NSAIDs, possibly short-course steroids, and avoidance of sitting.

Spinal stenosis is the congenital or acquired spinal canal narrowing that puts pressure on the spinal cord. It presents as lower back and leg pain, leg weakness, and pseudoclaudication that occurs after walking different distances while the vascularity of the legs remains intact. Pain is relieved by bending over or sitting. It is more common in those over 65 and its rules of evaluation are the same as for a herniated disc. It is initially treated with NSAIDs, physical therapy, and epidural corticosteroids.

Vertebral compression fractures are more common in older people and those with osteoporosis or chronic steroid use. This may happen after low-impact trauma or no trauma history at all. The pain is generally well localized to the spine and may be brought on by certain sudden movements. This is best initially evaluated by plain x-rays. It can be treated medically with pain control and with calcitonin or alendronate. Surgical management includes vertebroplasty or kyphoplasty.

Psychosocial factors and emotional distress should also be evaluated. Depression, fear avoidance (fear that activity will cause permanent damage), job dissatisfaction, current involvement in litigation, reliance on passive treatments, or somatization are predictors of slow recovery and increase the risk for developing chronic low back pain. Acknowledgement and management that includes treatment of such factors as applicable may be effective adjuvant therapy.

The vast majority of patients visiting a doctor for back pain will be diagnosed with **lumbar strain**. The exact anatomical cause of the pain is often unknown, but it is hypothesized that there may be an incomplete tear in the annulus fibrosus. This may leak fluids that create local inflammation or it may bulge posteriorly irritating certain lumbar roots. Irritation of the surrounding muscles, tendons, ligaments, or the joint capsule may be coconspirators in this painful process.

Treatment

The treatment of acute mechanical back pain (less than 4 weeks) centers on the use of NSAIDs, muscle relaxants, heat, and early mobility. No significant benefit has been observed with the use of opioids, corticosteroids, or greater than 2 days of bed rest. Specific exercises are also not found to be helpful. Massage therapy and spinal manipulation may be of some benefit for acute

pain; physical therapy has some benefit for short-term pain relief, but studies do not show long-term benefit. Traction has been shown to not be helpful mechanical back problems with or without sciatica. For prevention, exercise has been proven to help prevent back pain in certain subgroups of workers, but lumbar supports are shown not to prevent back pain.

Comprehension Questions

53.1 A 45-year-old man without significant past medical history presents with severe back pain after lifting boxes at work 2 days ago. Other than his back pain, his review of symptoms is negative. The pain radiates from his lower back down his posterior thigh to his great toe when you perform both a straight leg raise test and the contralateral leg raise. His strength, sensation, and reflexes are preserved. Which of the following imaging studies should be done immediately?

A. Plain radiographs
B. MRI
C. CT scan
D. No imaging indicated

53.2 A 75-year-old woman comes to her doctor complaining of low back pain for exactly 1 month after a fall. She has a history of diabetes, COPD, hypertension, osteoporosis, and breast cancer treated 3 years ago. She takes calcium supplements every day and alendronate. Which of the following characteristics would prompt further evaluation?

A. History of steroid use for COPD
B. Caucasian race
C. Time course of back pain
D. History of prior cocaine use
E. Premenopausal age

53.3 A 67-year-old man with coronary artery disease, dyslipidemia, and eczema comes to you complaining of lower back pain and leg pain. It is worse when he stands for long periods, but is better when he stoops to push his shopping cart around a store. He indicates that his feet "burn" and "ache" after walking different distances every day. Your examination of his nervous and muscular systems is normal. Which of the following is the best treatment for this patient?

A. Emergent spinal cord decompression
B. Steroid epidural injection
C. Kyphoplasty
D. Bed rest for 4 days

ANSWERS

53.1 **D.** The patient has signs and symptoms of a herniated disc. There is no evidence that imaging within the first month has any morbidity benefit. If symptoms persist after 1 month, then the MRI would be the correct choice. X-rays do not show disks or nerve roots, and CT has poorer visualization of soft tissue than MRI.

53.2 **A.** The patient's history is suspicious for a vertebral compression fracture that could be secondary to osteoporosis. Osteoporosis can be initiated by the use of steroids, which in this case was used to control her COPD. The time course of the pain is 4 weeks. Six weeks and greater is a red flag symptom for further evaluation. While osteoporosis is more common in Caucasian women, it is not considered a "red flag". Postmenopausal women are at greater risk for osteoporosis rather than premenopausal women.

53.3 **B.** The patient's history is classic for spinal stenosis. Often patients find relief by sitting or stooping. NSAIDs, physical therapy, and epidural steroid injections are used to relieve pain. Decompression is used in cauda equina syndrome and kyphoplasty is useful in vertebral fractures. Bed rest for more than 2 days is not used in the conservative treatment of back pain for any cause.

Clinical Pearls

- Red flag symptoms in low back pain should prompt an immediate diagnostic workup.
- Cauda equine syndrome is a surgical emergency that should be evaluated immediately by MRI.
- A herniated disc can be treated conservatively for 4 weeks before imaging has any proven benefit.
- Lumbar strain is common, generally resolves within a few weeks, and is treated with NSAIDs, muscle relaxants, and no more than 2 days of bed rest.

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Case 54

An 18-month-old male child is brought to your office by his mother for a routine well-child examination. This is his first visit to your office. According to his mother he has been seen for regular well-child examinations at another clinic since birth. The patient is the product of a term spontaneous vaginal delivery without complications. His medical history is unremarkable and his immunizations are up-to-date. No medical problems run in his family. He has one older sibling aged 6 with normal growth and development in the first grade. He lives at home with his parents and older sister. There are no pets in the home and no one smokes. Overall he eats a well-balanced diet, although mom reports he is sometimes a picky eater.

The patient's mother notes that she is concerned because he still does not use single words, and only babbles, and her other child was using many words by this age. On further history, you discover he often disregards the calling of his own name, but does startle to loud noises. The patient's mother has read about Autism on the internet and is concerned that her son may have this diagnosis. She also states that because of her concern, if he needs any immunizations today, she does not want them to be given for fear that this might worsen her son's condition.

On physical examination, the patient is 50th percentile for height, and 75th percentile for weight and head circumference. The rest of the physical examination is normal. On developmental examination you observe that he walks and runs well, and mom reports that he can walk up steps and kick a ball forward. Under your observation he only babbles and utters no words. Also, when given a toy car the patient puts it in his mouth but never demonstrates rolling the car along the floor or table. When you call the patient's name, tap him on the shoulder, say "Look!" and point to a toy in the corner you are unable to get his attention.

- By what age should an infant use single words?
- What is your next step in the evaluation of this patient?
- Should immunizations be delayed in this patient?

ANSWERS TO CASE 54:
Developmental Disorders

Summary: An 18-month-old child is brought in for a routine well-child examination and found to have a delay in language and social skill development.

- **Age by which a child should use single words:** Most children will say "mama/dada" indiscriminately by 9 months of age and use two words other than mama/dada by 12 months of age. No single words by 16 months of age are a red flag for the presence of an autism spectrum disorder (ASD).
- **Next step in evaluation of this patient:** Your screening of this patient notes developmental delays concerning for an autism spectrum disorder. You should complete your screening of this patient with a level 1 standardized autism-specific screening tool. Also, because of the concerns noted on examination you should immediately and simultaneously refer the patient for a comprehensive ASD evaluation, early intervention/early childhood education services, and an audiologic evaluation.
- **Timing of immunizations:** There is no evidence that immunizations are implicated as a cause of autism and thus the parents should be counseled that the routine immunizations are recommended. Concerns have been raised in the past that the MMR vaccine may precipitate autism based on reports of parents who first detected autism in their children following MMR vaccination and an anecdotal study of 12 autistic patients in which their physicians reported similar suspicions. However, subsequent studies have failed to show convincing evidence of a link between MMR vaccination and the development of autism. Also, there is no evidence to support that the use of thimerosal (a mercury-containing preservative) in vaccines causes autism.

ANALYSIS

Objectives

1. Learn the diagnostic criteria for autism spectrum disorders and the differential diagnosis of pervasive developmental delay.
2. Know the key clinical signs of autism spectrum disorders (ASDs).
3. Be able to formulate a strategy for the assessment of ASDs.

Considerations

This 18-month-old child presents with significant language delay and social skills delay. These two findings are very suspicious for autism spectrum disorder (ASD). There is no description of stereotyped movement or findings, but

these are not necessary for the diagnosis of ASD. However the child should also have a hearing screening examination. Because he startles to loud noise, significant hearing deficit is not likely. This child should have a comprehensive autism assessment.

APPROACH TO
Pervasive Developmental Disorders

DEFINITIONS

JOINT ATTENTION: An infant demonstrates enjoyment in sharing with another individual an object/event by looking back and forth between the individual and the object/event.

SOCIAL RELATEDNESS: Internal drive to connect with others and share similar feelings.

CLINICAL APPROACH

Autism spectrum disorders (ASDs) include three of the pervasive developmental disorders identified in the DSM-IV and include autistic disorder (AD), Asperger syndrome (AS), and pervasive developmental disorder-not otherwise specified (PDD-NOS).

According to the most recent studies, the **prevalence of ASDs is about 6 per 1000**. More boys are affected than girls, with the prevalence four times as high for males as compared to females. Family studies also estimate a recurrence risk of as much as 5% to 6% when there is an older sibling with an ASD.

As evidenced by the prevalence of ASDs, most physicians will care for several children during the course of their career with an ASD. Furthermore, as a result of increased media attention intended to raise awareness about these disorders and the early signs, more and more parents will begin to raise concerns to their child's physician. Primary care physicians must be able to recognize the key clinical features of these disorders, be able to formulate a systematic plan to assess them, and know how to assist families with the ongoing treatment and care of a child with an ASD.

ASDs are phenotypically heterogenous neurodevelopmental disorders that are the result of a combination of factors. Evidence supports multiple gene involvement with environmental factors influencing the wide variation in phenotypic expression. Environmental factors implicated include exposures to teratogens in utero and maternal illnesses during pregnancy, but no studies have verified a causal role.

Common features shared by all the ASDs include severe deficits in social skills and limited, repetitive, and stereotyped behavior patterns. However, only AD and PDD-NOS are characterized by significant language delays.

Although there is no pathognomotic feature, ASDs are universally characterized by deficits in social relatedness, and the early social deficits, such as delayed or absent joint attention appear to be reliable red flag symptoms. However, these characteristics frequently go unnoticed by parents and it is a delay in speech that prompts them to raise a concern with their child's physician.

In order to diagnose autistic disorder, a child must demonstrate abnormal behavior before age 3 and must have delays in the areas of social interaction, language used for social communication, and symbolic or imaginative play. Deficits include the following:

1. **Impaired social interaction:**
   a. Deficient use of nonverbal behaviors such as facial expressions, eye contact, and gestures.
   b. Lack of peer relationships appropriate to developmental age.
   c. Does not spontaneously seek social relatedness through shared emotions, interests, or achievements with others.
2. **Impaired communication:**
   a. Delay in/lack of spoken language development.
   b. If the child does have adequate speech, there is an impaired ability to sustain or begin a conversation with others.
   c. Repetitious, scripted, or stereotyped use of language.
   d. Lack of, or severely delayed pretend play skills.
3. **Restricted, repetitive, and stereotyped patterns of behavior, interests, and activities**:
   a. Repetitive, nonfunctional, atypical behaviors such as hand flapping, finger movements, rocking, and twirling.
   b. Restricted patterns of interest that is atypical in either intensity or focus.
   c. Inflexible adherence to nonfunctional rituals.
   d. Preoccupations with parts of objects.

Children with Asperger Syndrome (AS) may go unnoticed until they are school age and begin to demonstrate difficulties with peer and teacher interaction. Children with AS have only mild or limited speech delay, but if observed closely their language has often developed atypically. These children show deficits in the use of social language, such as choosing a topic of conversation, tempo, facial expression, and body language. Speech is also often pedantic and limited to only a few topics that hold an all-consuming interest to the child.

Neurogenetic comorbid conditions and mental retardation have also been found to be associated with ASDs, although the most recent data indicate the percentages to be much less than previously thought, 10% and 50%, respectively. Neurogenetic syndromes that may play a causative role in ASDs or otherwise may be associated, as well as other PDDs, must be considered in a clinician's differential diagnosis. These are included in Table 54–1.

Table 54–1 NEURODEVELOPMENTAL CONDITIONS ASSOCIATED WITH ASDS

CONDITION	ETIOLOGY	CHARACTERISTICS
Rett syndrome	X-linked dominant disorder (fatal to male fetus)	Microcephaly, seizures and hand-wringing stereotypies
Childhood disintegrative disorder	Unknown	Normal development until 2-4 y, then severe deterioration of motor and social functioning
Fragile X syndrome	Most common genetic cause of AD and retardation in males	Mental retardation, macrocephaly, large pinnae, large testicles, hypotonia, and hyperextensible joints
Neurocutaneous disorders		
Tuberous sclerosis	Autosomal dominant, but most cases are new mutations	Hypopigmented macules, fibroangiomata, kidney lesions, CNS hamartomas, seizures, MR, ADHD
Neurofibromatosis	Autosomal dominant, half of cases are new mutations	Café-au-lait spots, axillary freckling, neurofibromas, ocular Lisch nodules
Phenylketonuria	Inborn error of metabolism	Routinely tested for by newborn screening; MR/AD preventable with dietary modification
Fetal alcohol syndrome	Exposure to alcohol in utero	Characteristic facies; associated with AD and other developmental disorders
Angelman syndrome	Loss of maternally expressed ubiquitin-protein ligase gene	Global developmental disorder, hypotonia in early childhood, wide-based ataxic gait, seizures, and progressive spasticity
Childhood schizophrenia	Unknown	Thought disorder, delusions, and hallucinations

Treatment

The key to successful treatment of ASDs is early diagnosis leading to early intervention. **Surveillance for ASDs should occur at every preventative visit throughout childhood**, and includes eliciting a family history of ASDs, parental and other caregiver concerns, developmental history, and making accurate observations of the child. **All children should also be screened with a standardized developmental tool at the 9-, 18-, and 24- or 30-month visits**. If concerns for an ASD are raised during one of these visits, then a screening tool specifically designed for ASDs should be used. Available screening tools include the checklist for autism in toddlers (CHAT) and the modified-CHAT for children 18 months of age or older. Before 18 months of age, screening tools that target social and communication skills may be helpful for detecting early signs of ASDs. If no concerns have been raised during routine preventative visits, ASD-specific screening is indicated only at the 18- or 24-month preventative visit. **Red flag symptoms indicating the need for immediate evaluation include:**

- No babbling or pointing by 12 months
- No single words by 16 months
- No 2-word phrases by 24 months
- Loss of language or social skills at any age

When a child demonstrates two or more risk factors or a positive screening result occurs, take immediate action. Do not just "wait-and-see." The following steps should be accomplished simultaneously:

- Refer the child for a comprehensive ASD evaluation.
- Refer the child to early intervention/early childhood education services.
- Obtain an audiologic evaluation.

Children with ASDs who begin treatment at a younger age have significantly better outcomes, making early identification and intervention critical. The goals of treatment are to improve language and social skills, decrease maladaptive behaviors, support parents and families, and foster independence.

Comprehension Questions

54.1 A mother brings her 5-year-old son to your office because his teacher is concerned that he has attention-deficit hyperactivity disorder (ADHD). The teacher has noticed the child frequently makes long-winded speeches about boats in class and is often rocking back and forth in his seat. On further history taking, the child's mother states that he is very independent with few friends, and has always been interested in boats, preferring them over all other toys. You observe that his speech is monotone and restricted in volume and rate and he never makes eye contact with you or his mother. Which of the following statements is most accurate regarding this child?

A. An Asperger-specific screening tool appropriate for the child's age is the next important step.
B. The most important issue for today's visit is to administer vaccinations the child is missing.
C. This child should be started on oral amphetamine-like compounds, which will likely lead to much improved behavior.
D. This parent should be reassured, as this child's behavior and development is most likely a variant of normal.
E. It is probable that one of the vaccinations is responsible for this child's clinical findings.

54.2 Which of the following statements is accurate?

A. A previously healthy, normally developing 3-year-old child begins to lose bladder control and will no longer speak in sentences, but you should not be too concerned because this began after the birth of her younger sibling and she just wants more attention from her parents.
B. No use of single words by 12 months of age in a child is reason for immediate referral to speech therapy.
C. Children with ASDs will rarely grow up to be independent adults.
D. You counsel the parents of a 6-year-old son with autism that their second child is at increased risk for having an ASD.

54.3 Which of the following observations during a clinical examination is concerning for the presence of an ASD?

A. You walk into the examination room and find a 36-month-old child pretending to have tea with her imaginary friend.
B. A 12-month-old child walks over to the sink, and points toward the faucet, but only utters, "Uh," and does not say water.
C. A 2-year-old child is holding tightly to a tattered old blanket, which his mother says he will not leave the house without.
D. You tap an 18-month-old child on the shoulder, say, "Look!" and point to a toy in the corner of the room, but the child ignores you and continues to spin the wheels on his toy car.

ANSWERS

54.1 **A.** While at first glance the concerns of this child's teacher and mother may sound typical for ADHD, your clinical suspicion should be that the child has Asperger syndrome, based on a history of monotone, restricted speech limited to only one topic of interest, lack of eye contact, lack of peer relationships appropriate to developmental age, and the repetitive, nonfunctional, atypical behavior of rocking and twirling. Appropriate steps at this time include a complete history and physical examination accompanied by an Asperger-specific screening tool and immediate referral to a developmental pediatrician for a complete evaluation. You should reassure the child's mother that immunizations are not implicated in the cause of developmental disorders and administer any vaccines needed. You should not delay your diagnostic workup for a developmental disorder for any reason. Although immunizations are important, for this child's situation, evaluation of the developmental problems is of higher priority.

54.2 **D.** Family studies estimate a recurrence risk of as much as 5% to 6% when there is an older sibling with an ASD. Red flag symptoms indicating the need for an immediate evaluation for an ASD include loss of language or social skills at any age and no use of single words by 16 months of age. Although most children with an ASD will retain their diagnosis and exhibit residual signs of their disorder into adulthood, children with ASDs who begin treatment at a younger age have significantly better outcomes, and one of the goals of treatment is to foster independence.

54.3 **D.** The child in answer choice (D) demonstrates a deficit in joint attention, one of the most distinguishing characteristics of very young children with ASDs. It is the lack of pretend play skills, rather than their presence (choice A), that is concerning for an ASD. As demonstrated in answer choice (B) at about 12 to 14 months of age, a typically developing child will begin to request a desired object that is out of reach by pointing, and, depending on the child's speech skills, may utter simple sounds or actual words. Similar to answer choice (C) most children will form attachments during their early development with a stuffed animal, special pillow or blanket. However, children with ASDs may prefer hard items such as ballpoint pens, keys, or flashlights.

Clinical Pearls

- Common features shared by all the ASDs include severe deficits in social skills and limited, repetitive, and stereotyped behavior patterns. However, only AD and PDD-NOS are characterized by significant language delays.
- Red flag symptoms indicating the need for immediate evaluation for an ASD include: no babbling or pointing by 12 months, no single words by 16 months, no 2-word phrases by 24 months, and loss of language or social skills at any age.
- When a child demonstrates two or more risk factors or a positive screening result occurs, take immediate action.

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Case 55

A 46-year-old woman presents to your office complaining of a hand tremor that has been steadily worsening over the past 2 years. She works as a literary agent and states that this tremor is increasingly impairing her ability to work. She tells you in a slightly quivering voice, "I am often required to take my clients out to lunch, and I get embarrassed when I cannot eat and drink normally. Sometimes, I cannot even drink from a cup without shaking." She finds that a glass of wine with her meal sometimes helps. On examination, her blood pressure is 125/85 mm Hg, her pulse is 84 beats/min, and her respiratory rate is 16 breaths/min. Neurologic examination reveals a mild head tremor, but no resting tremor of the hands. When she holds a pen by its tip at arm's length, however, a coarse tremor becomes readily visible. The rest of her examination is normal.

- What is the most likely diagnosis?
- What further evaluation needs to be performed?
- What pharmacologic interventions may be beneficial?

ANSWERS TO CASE 55:
Movement Disorders

Summary: A 46-year-old woman presents with a classic essential tremor. It comes on during action and remits when the limb is relaxed, unlike the tremor of Parkinson disease. She is very disturbed by the tremor as it is leading to a great deal of social embarrassment, often interfering with her work. She has found that alcohol helps to reduce the symptoms.

- **Most likely diagnosis:** Essential tremor.
- **Further evaluation necessary:** Ensure that medications, thyroid disease, alcohol, or other neurologic diseases are not causing the tremor.
- **Beneficial pharmacotherapy:** Propanolol, primidone, and gabapentin.

ANALYSIS

Objectives

1. Become familiar with the presenting signs and symptoms of the most common movement disorders.
2. Become familiar with the management of common movement disorders.
3. Be able to gauge the severity of disease and understand side effects of therapies.

Considerations

Essential tremor is the most common of all movement disorders, affecting 1.3% to 5% of persons over the age of 60. A complete history is crucial in making the diagnosis of essential tremor. It usually appears after the age of 50 and interferes with common tasks and activities of daily living. Many patients have a family history of tremor, although this is not a criterion for diagnosis. It is often attenuated with the use of alcohol. It is important to ask about the consumption of caffeine, cigarette smoking, stimulant use, and inquire about other medications (eg, inhaled β-agonists, levothyroxine, lithium) that are known to cause or enhance physiologic tremor. When essential tremor is suspected, the patient should be observed while performing common tasks such as drinking from a glass. It affects the hands in 95%, the head in 34%, and the lower extremities in 20% of patients. When patients under the age of 40 years present with an action tremor, they should also be evaluated for Wilson disease, a disorder of copper metabolism.

Pharmacotherapy constitutes the main approach to treatment. First-line therapies include the β-blocker propanolol and the anticonvulsant primidone. They are equally efficacious in reducing tremor symptoms. Gabapentin is another anticonvulsant which can be used as a second-line agent, although

experience is limited. The patient's report of symptoms and functional ability, rather than the severity of tremor detected on physical examination, should serve as guides for adjustment of therapy. It is also important to monitor patients for side effects of these medications. Propanolol is associated with fatigue, headaches, bradycardia, impotence, and depression. Primidone can cause an acute reaction consisting of nausea, vomiting, or ataxia in many patients.

As with therapy for Parkinson disease, both deep brain stimulation and ablation of the ventral intermediate nucleus of the thalamus (Vim nucleus) are effective in patients with tremor that is refractory to medical treatment.

APPROACH TO Movement Disorders

DEFINITIONS

CHOREA: Unpredictable, irregular, brief movement that are jerky, writhing, or flowing.

HYPERKINESIAS: Movement disorders characterized by extra or exaggerated movements.

HYPOKINESIAS: Movement disorders characterized by overall slowness of movement (bradykinesia), lack of movement (akinesia), or difficulty in initiating movement.

CLINICAL APPROACH

A movement disorder can be defined as any condition that disrupts normal voluntary movement of the body or that consists of one or more abnormal movements. They can be classified as hypokinesias or hyperkinesias (see Table 55–1).

Table 55–1 CLASSIFICATION OF MOVEMENT DISORDERS

HYPOKINETIC DISORDERS	HYPERKINETIC DISORDERS
Parkinson disease	Tremor (essential tremor, dystonic tremor, drug-induced tremor, physiologic tremor)
Secondary or acquired parkinsonism (can be caused by neuroleptics, hydrocephalus, head trauma)	Tic disorders (Tourette syndrome)
Progressive supranuclear palsy (PSP)	Chorea (Huntington disease)
Multiple system atrophy (Shy-Drager syndrome, olivopontocerebellar atrophy, striatonigral degeneration)	Myoclonus
	Dystonia
	Ataxia

Though less frequently encountered by family physicians than other chronic diseases, they are fairly common, especially in the elderly population. Parkinson disease, for example, affects 1% of those over 65 and 2% of those over 85 years of age.

Movement disorders present a special challenge to family physicians for many reasons. Signs and symptoms can often be subtle. The normal process of aging is associated with changes in movement that may be mistaken for a more serious problem. Patients suffering from the same movement disorder can often present in a variety of different ways. Finally, **laboratory and radiologic testing is often of limited value in the diagnosis of movement disorders.**

Management is equally challenging. Movement disorders have a great impact on other medical conditions as well as on the psychological well-being of patients and their families. Although pharmacotherapy and surgeries are often administered by specialists, family physicians must help patients cope with the broad impact of their disease.

Parkinson Disease

Parkinson disease is the most common neurodegenerative disease, and can cause significant disability and decreased quality of life. Symptoms appear as neurons and dopamine are lost from the substantia nigra and intracytoplasmic inclusions (Lewy bodies) proliferate. The **cardinal physical signs of the disease are distal resting tremor, rigidity, bradykinesia, postural instability, and asymmetric onset**. Although not a "classic" feature, patients also have a positive glabella tap reflex.

Pharmacotherapy is the mainstay of treatment for Parkinson disease, and has been shown to reduce morbidity and mortality. The goals are twofold: the protection of neurons to slow down or stop disease progression and symptomatic therapy. **Levodopa is the primary treatment for Parkinson disease**, although its long-term use is limited by motor complications, drug-induced dyskinesia, and psychosis. Levodopa is given in combination with carbidopa, which prevents the peripheral destruction of levodopa and allows it to cross the blood-brain barrier.

Dopamine agonists such as bromocriptine, pergolide, and pramipexole are options for initial treatment and have been shown to delay the onset of motor complications. However, they are inferior to levodopa in controlling motor symptoms. It is often beneficial to initiate adjuvant therapy with dopamine agonists, catechol O-methyltransferase inhibitors, or monoamine oxidase-B inhibitors after levodopa-related motor complications develop in advanced Parkinson disease. Deep brain stimulation of the subthalamic nucleus has been shown to ameliorate symptoms in patients with advanced disease. Common psychiatric problems associated with Parkinson disease include depression, dementia, and psychosis. Psychosis is usually drug-induced and can be managed initially by reducing the dose of antiparkinsonian medications. Consultation with a subspecialist is often required.

Since the functional impairment of Parkinson disease is progressive, discussion of advance directives is appropriate with all patients. Education and support are important ways patients can cope with their illness.

Tourette Syndrome

Tourette syndrome is the most common tic disorder, usually developing during childhood or early adolescence. Heredity is thought to play a major role in its etiology. The diagnosis requires the presence of multiple motor and one or more vocal tics, tics occurring several times a day for at least 1 year, onset before age 21, and having tics that cannot be explained by other medical conditions. There are a number of different types of tics and they may worsen during periods of stress, excitement, boredom, or fatigue. The majority of affected children also suffer from coexisting attention-deficit hyperactivity disorder (ADHD), obsessive-compulsive symptoms, or migraine headaches.

Pharmacotherapy is the mainstay of treatment and should only be started if there is functional impairment. The dopamine receptor blockers haloperidol and pimozide are widely used and very effective treatments for tics. The α-receptor agonists clonidine and guanfacine are effective for treating mild tics. Both also help improve symptoms of accompanying ADHD. Treatment of accompanying ADHD and obsessive-compulsive symptoms is absolutely essential.

Huntington Disease

The most common cause of chorea among adults occurs in Huntington disease. **Huntington disease is inherited in an autosomal dominant pattern**, and affects men and women in equal numbers. It is caused by a genetic mutation of the IT15 gene located on chromosome 4b. Onset may be at any age, though symptoms first appear between 35 to 50 years of age. There are two types of movement abnormalities: chorea and abnormal voluntary movements. The latter include uncoordinated fine motor movements, gait disturbances, abnormal eye movements, dysarthria, dysphagia, and rigidity. Difficulties with voluntary movements get worse with time. Cognitive problems include difficulties with memory, visuospatial abilities, and judgement. A global dementia may be present in patients with advanced disease. The most common psychiatric problem is depression, which affects up to 40% of patients. Almost 13% of patients commit suicide.

There is **currently no treatment available to slow the progression of disease**. Treatment should target the signs and symptoms, and be adjusted according to disease severity. The chorea does respond favorably to haloperidol and fluphenazine, though such treatment often makes voluntary movements worse. The chorea can also be treated with reserpine, tetrabenazine, and clonazepam. Depression should be aggressively treated with conventional antidepressants such as SSRIs. The primary counseling responsibility of the family physician is to understand the role of genetic testing and to offer it to affected and asymptomatic individuals in a responsible manner.

Comprehension Questions

55.1 An 18-year-old adolescent male patient is noted to have motor tics and involuntary, obscene vocalizations. Which of the following medications is most effective in the treatment of this disorder?

A. Trihexyphenidyl (Artane)
B. Phenytoin (Dilantin)
C. Carbamazepine (Tegretol)
D. Haloperidol (Haldol)
E. Levodopa

55.2 A 21-year-old woman develops auditory hallucinations and persecutory delusions over the course of 3 days. She was hospitalized and started on haloperidol 2 mg three times daily. Within a week of treatment, she developed stooped posture and a shuffling gait. Her head was slightly tremulous and her movements became slowed. Her medication was changed to thioridazine (Mellaril), and trihexyphenidyl (Artane) was added. Over the next 2 weeks, she became much more animated and reported no recurrence of her hallucinations. Which of the following is the most likely diagnosis?

A. Hyperparathyroidism
B. Neuroleptic effect
C. Encephalitis
D. Hypermagnesemia

55.3 Which of the following represents the decrement in speech commonly exhibited by the patient with parkinsonism?

A. Progressively inaudible speech
B. Neologisms
C. Expressive aphasia
D. Receptive aphasia
E. Word salad

55.4 A 67-year-old woman with known Parkinson disease is brought to the clinic by her health-care provider. She is confined to a wheel chair and completely dependent on others. You notice large grossly abnormal movements in both the arms and legs. The patient has to be strapped in to avoid falling out and can't keep her shoes on. Bed rails have had to be installed on her bed to prevent her from falling out at night. She does not know the month or the year. She has not had a change in her medication in 6 months. Which of the following medication adjustments would benefit her most?

A. Add Haloperidol
B. Decrease Levodopa/Carbodopa
C. Increase Levodopa/Carbodopa
D. Add Donepezil
E. Add Entacapone

ANSWERS

55.1 **D.** The clinical scenario described is that associated with Tourette syndrome. A variety of drugs may help suppress the tics that are characteristic of this syndrome. These include haloperidol, pimozide, trifluoperazine, and fluphenazine. Antiepileptics, such as carbamazepine and phenytoin, are not useful. Trihexyphenidyl and benztropine are useful in suppressing the parkinsonism that may develop with haloperidol administration, but are not useful in the management of Tourette syndrome.

55.2 **B.** Butyrophenones, the most commonly prescribed of which is haloperidol, routinely produce some signs of parkinsonism if they are used at high doses for more than a few days. This psychotic young woman proved to be less sensitive to the parkinsonian side effects of the phenothiazine thioridazine than she was to haloperidol. Adding the anticholinergic drug trihexyphenidyl may have also helped to reduce the patient's symptoms.

55.3 **A.** Language is not disturbed in Parkinson disease, as it is with aphasias. The clarity and volume of speech is what suffers. Handwriting is similarly disturbed, as the patient has increasingly smaller and less legible penmanship as he or she continues to write. This is referred to as micrographia.

55.4 **B.** The patient is suffering from dyskinesias from too much levodopa/carbodopa. A reduction in these medications would be of the most benefit to her. Haloperidol would be a good choice if the patient was suffering from hallucinations. Donepezil is a medication used primarily for Alzheimer dementia and has no use in Lewy Body dementia. Entacapone is a medication to enhance levodopa/carbodopa.

Clinical Pearls

- Movement disorders have a profound impact on the quality of life of patients and their families. Family physicians should become adept at counseling patients about prognosis and the availability of support groups and community resources.
- The management of certain movement disorders including Parkinson disease is rapidly changing. It is important to find the latest information about emerging and alternative therapies, and to seek the help of a specialist when required.

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SECTION III

Listing of Cases

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Listing by Case Number

Listing by Disorder (Alphabetical)

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