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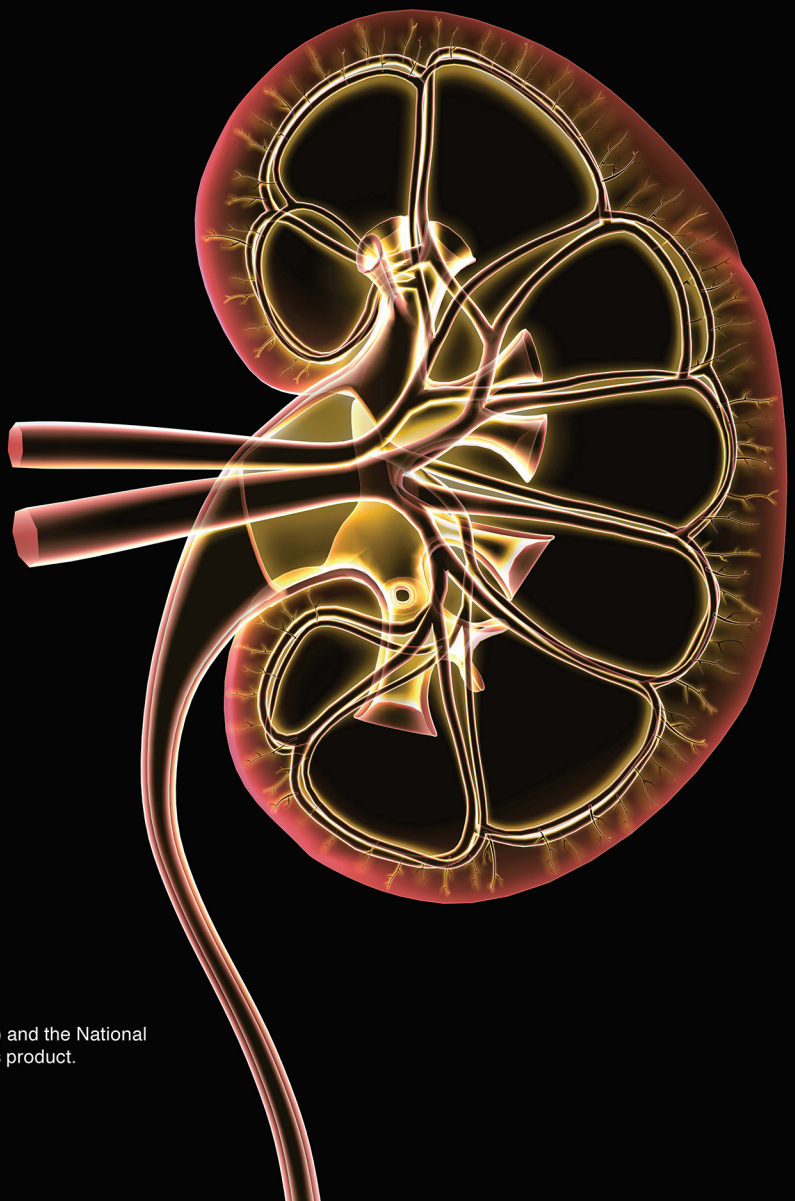
Lecture Notes 2021



Internal Medicine

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Step 2 CK

Lecture Notes

2021

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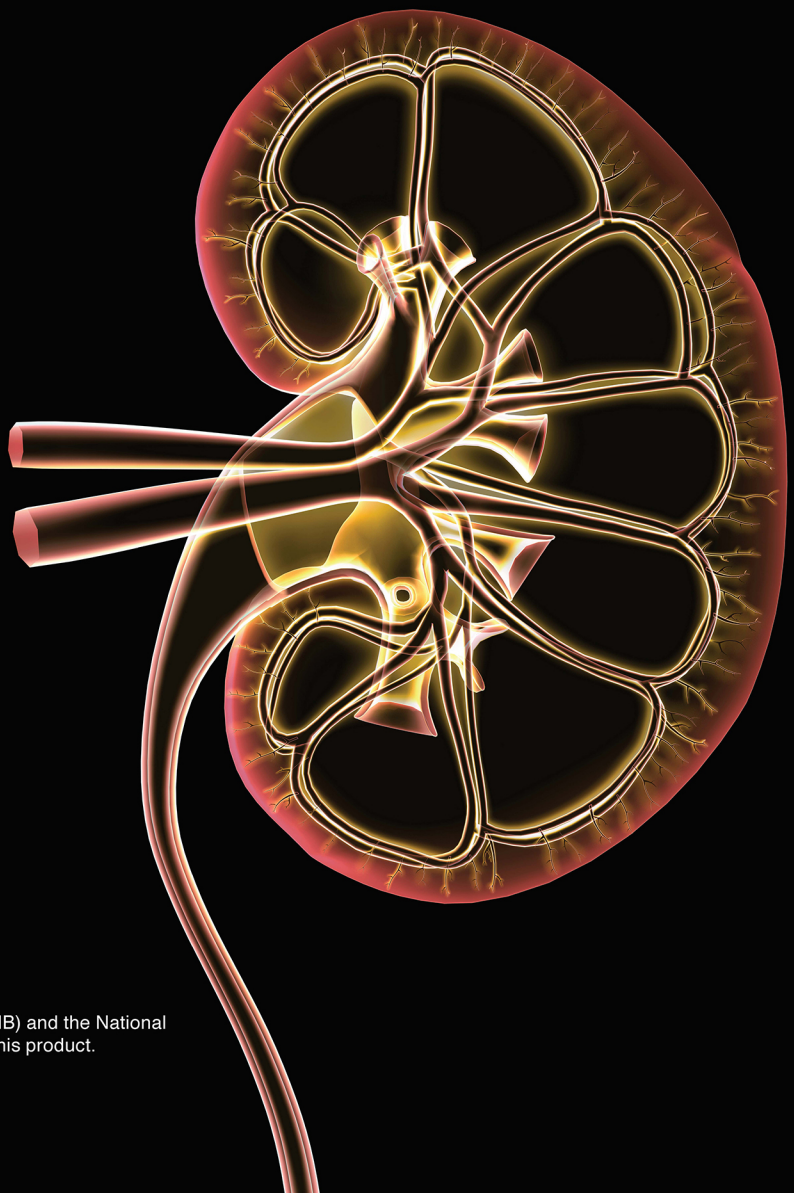

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1 Preventive Medicine

Learning Objectives

- ❑ Describe appropriate screening methods as they apply to neoplasms of the colon, breast, cervix, and lung
- ❑ Describe epidemiological data related to incidence and prevention of common infectious disease, chronic illness, trauma, smoking, and travel risks

SCREENINGS

For all diseases that have recommended screening:

- Effective intervention must exist
- After a positive test result, course of events must be acceptable to patient
- Screening test must be valid, i.e., it must have proven in trials to decrease overall mortality

For a screening test to be recommended for regular use, it has to be extensively studied to ensure that all of the above requirements are met.

Cancer Screening

A 39-year-old woman comes to the clinic very concerned about her risk of developing cancer. Her father was diagnosed with colon cancer at age 43, and her mother was diagnosed with breast cancer at age 52. She is sexually active with multiple partners and has not seen a physician since a car accident 15 years ago. She denies any symptoms at this time, and her physical examination is normal. She asks what is recommended for a woman her age.

Screening tests are done on seemingly healthy people to identify those at increased risk of disease.

However, even if a diagnostic test is available, that does not always mean it should be used to screen for a particular disease. That is because diagnostic tests may:

- Have adverse (and possibly iatrogenic) effects (e.g., large bowel perforation secondary to a colonoscopy)
- Be expensive, unpleasant, and/or inconvenient
- Lead to ineffective or even harmful treatment

The 4 malignancies for which regular screening is recommended are **cancers of the colon, breast, cervix,** and **lung**.

Colon Cancer

If there is no significant family history of colon cancer, screen everyone starting age 50.

- Colonoscopy every 10 years (**preferred**)
- Annual fecal occult blood test and sigmoidoscopy with barium enema every 5 years

If there is a single first-degree relative diagnosed with colorectal cancer age <60 or multiple first-degree relatives with colon cancer at any age, screen with colonoscopy starting age 40 or 10 years before the age at which the youngest affected relative was diagnosed, **whichever age occurs earlier.**

- Repeat colonoscopy every 5 years
- Routine screening can stop age >75, as per the U.S. Preventive Services Task Force (USPSTF)

Note

Tamoxifen prevents cancer by 50% in those with >1 family member with breast cancer.

Breast Cancer

Mammography plus manual breast exam are used to screen for breast cancer. (Self-breast exam by itself is not recommended as a screening tool.)

- Mammography with or without clinical breast exam every 1–2 years from age 50–74
- If there is a very strong family history of breast cancer (i.e., multiple first-degree relatives), consider prophylactic tamoxifen, which prevents breast cancer in high-risk individuals

Note

Prostate Screening

USPSTF concludes that the current evidence is insufficient to assess the balance of benefits/risks of prostate cancer screening in men age <75. It recommends against screening in men age >75.

For USMLE, do not screen for prostate cancer.

Cervical Cancer

The screening test of choice for the early detection of cervical cancer is the Papanicolaou smear (the "Pap" test). In average risk women, screen as follows:

- Starting age 21, screen with Pap (regardless of onset of sexual activity) every 3 years until age 65
- Alternatively, screen with Pap + HPV testing every 5 years, age 30–65
- Higher risk women, e.g., HIV, may require more frequent screening or screening age >65

Lung Cancer

Current recommendations for lung cancer screening are as follows:

- For adults age 55–80 with a 30-pack-year smoking history and currently smoke or have quit within 15 years, screen annually with low-dose CT.
- For those who have not smoked for 15 years; age >80; or who have another medical problem which significantly limits life expectancy or the ability to undergo surgery, screening is not necessary.

Clinical Recall

Which of the following patients is undergoing an inappropriate method of screening as recommended by the USPSTF?

A. A 50-year-old man gets his first screening for colon cancer via colonoscopy

B. A 50-year-old woman gets her first screening for breast cancer via mammography

C. A 17-year-old woman is screened for HPV via a Pap smear after her first sexual encounter

D. A 65-year-old man with a 30-pack-year smoking history gets a low-dose CT

E. A 21-year-old woman with a high risk of developing breast cancer is given tamoxifen

Answer: C

Osteoporosis Screening

A bone density test uses x-rays to measure how many grams of calcium and other bone minerals are packed into a segment of bone. The bones typically tested are the spine, hip, and forearm.

- Screening with a DEXA bone density scan should be given to all women age >65.
- Screening should begin at age 60 if there is low body weight or increased risk of fractures.

Bone density test results are reported in 2 numbers.

- The **T-score** compares the patient's bone density with what is normally expected in a healthy young adult of the same sex. This score is the number of units—standard deviations—that bone density is above or below the average.
  - T-score >2.5 SD indicates the likelihood of osteoporosis and increased risk of fracture.
  - A diagnosis of osteoporosis by DEXA scan also means that treatment should be initiated with bisphosphonates, oral daily calcium supplementation, and vitamin D.

Note

A **pack year** is smoking an average of 1 pack of cigarettes per day for 1 year. A patient with a smoking history of 30 pack years is considered a heavy smoker.

Note

Low bone density is very common among older adults, so **Z-score** can be misleading.

- Use Z-score (not T-score) for children/teens/women of childbearing age/ younger men.
- In these younger age groups, routine bone density screening is not recommended, nor should a diagnosis of osteoporosis be based on bone density test alone.

- The **Z-score** compares the condition of the patient's bones with those of an average person the same age and body size. It is the number of standard deviations above or below what is normally expected for someone of the same age, sex, weight, and ethnic or racial origin.
  - Z-score ≤-2 may suggest that something other than aging is causing abnormal bone loss (consider drugs causing osteoporosis such as corticosteroids).
  - The goal in this case is to identify the underlying problem.

Hypertension, Diabetes Mellitus, and Hypercholesterolemia

> A 45-year-old man comes to the physician anxious about his health. Five years ago his mother was diagnosed with diabetes and high cholesterol. He is worried about his health and risk for heart disease. Physical examination is within normal limits.

Cholesterol screening should commence at age 35 in men who have no risk factors for coronary artery disease. In both men and women with risk factors, screening should be done routinely after age 20. Management should not be determined by an isolated reading because cholesterol levels may fluctuate between measurements. Repeat in 5 years in low-risk individuals.

Screening for diabetes mellitus should be considered only for patients with hypertension (>135/80 mm Hg). Diabetes mellitus is diagnosed in either of these situations:

- Two fasting glucose measurements are >125 mg/dL, HbA1c >6.5%
- Random glucose >200 mg/dL accompanied by symptoms

There is insufficient evidence for or against routine screening. The strongest indication is for those with hypertension and hyperlipidemia.

Screening is recommended for elevated blood pressure in those age >18, at every visit. Screening is not recommended for carotid artery stenosis with duplex.

Abdominal Aortic Aneurysm

U/S should be done once in men age >65 who have ever smoked. There are no screening recommendations for male nonsmokers and women, regardless of smoking history.

TRAVEL MEDICINE

> A 44-year-old man comes to the clinic before traveling to Thailand for business. He has no significant past medical history and is here only because it is required by his company. The patient appears agitated and demands the physician's recommendation immediately.

It is important to set up a pretravel counseling session 4–6 weeks before the patient's departure.

Recommendations are as follows:

- **Hepatitis A** vaccination: recommended for all travelers to less developed nations
  - If patient is departing within 2 weeks of being seen, give both the vaccine and immune serum globulin
  - Booster shot given 6 months post-initial vaccination provides immunity for approximately 10 yrs
- **Hepatitis B** vaccination: recommended for patients who work closely with indigenous populations
  - If patient plans to engage in sexual intercourse with the local populace or to receive medical/dental care, vaccinate
  - If patient plans to remain abroad for >6 months, vaccinate
- **Malaria**
  - Mefloquine is the agent of choice for malaria prophylaxis (given 1×/week); side effects include neuropsychiatric effects such as hallucinations, depression, and unusual behavior
  - Doxycycline is an acceptable alternative; side effects include photosensitivity
  - In pregnancy, chloroquine is the preferred regimen for prophylaxis
- **Rabies** vaccination is recommended only for those traveling to areas where rabies is common among domesticated animals (India, Asia, Mexico). It is not considered a routine vaccine for most travelers.
  - Chloroquine can blunt the response to the **intradermal** form of rabies vaccine
  - Therefore, if both malaria prophylaxis and rabies prophylaxis are required, give the intramuscular form of the vaccine
- **Typhoid** vaccination is recommended for those traveling to developing nations, who may have prolonged exposure to contaminated food and water; side effects include irritation at the injection site and rarely headache and fever
  - Live attenuated form: given orally (needs refrigeration; contraindicated for HIV patients)
  - Capsular polysaccharide form (**preferred**): given intramuscularly 1× (needs no refrigeration; safe for HIV patients; well-tolerated)

Polio vaccination is recommended for those traveling to developing nations.

- If patient has not previously received a polio vaccine, give 3 doses of the inactivated polio vaccine.
- If patient has previously been immunized, give a one-time booster.
- The live attenuated polio vaccine is no longer recommended because of the risk of vaccine-associated disease.

Note

- The global health approach to disease prophylaxis is to provide treatment to travelers whose destination is an area where the disease is endemic.
- Because disease distribution shifts over time, country-specific questions are not likely to be on the exam.

Note

Hepatitis A infection is the most common vaccine-preventable disease in travelers. It can occur wherever there is fecal contamination of food/drinking water.

Other general travel recommendations are as follows:

- **Polysaccharide vaccination** is recommended for those traveling to areas where meningococcal meningitis is endemic or epidemic (Nepal, sub-Saharan Africa, northern India).
  - Meningococcal vaccine is now routinely administered at age 11
  - Saudi Arabia requires immunization for pilgrims to Mecca
  - Immunize those with functional (or actual) asplenia and those with terminal complement deficiencies
- To prevent **traveler's diarrhea**, patients should be advised to avoid raw and street vendor salads, unwashed fruit, and tap/ice water. Patients who experience mild loose stools without fever or blood can safely take loperamide. Treatment with a fluoroquinolone or azithromycin is reserved for patients with moderate to severe symptoms.

IMMUNIZATIONS

> A 52-year-old man comes to the clinic for a health maintenance evaluation. His recent colonoscopy showed no evidence of carcinoma. Recent serum fasting glucose, serum cholesterol, and blood pressure are all within normal limits. The patient has a history of smoking and continues to smoke 2 packs per day. He was diagnosed with COPD 3 years ago.

Immunization is the best method available for preventing serious infectious disease. Between 50,000–70,000 adults die every year from preventable infectious disease (influenza, invasive pneumococcal disease, and hepatitis B).

Surveys have shown that among patients who have an indication for any vaccination, very few actually receive it (pneumococcal vaccination 20%, influenza 40%, hepatitis B 10%). For this reason, the American College of Physicians recommends that **every patient's immunization status be reviewed at age 50**; evaluate risk factors for specific vaccinations at that time.

- Most patients received a primary immunization against tetanus and diphtheria as children.
- For those adults who were never vaccinated, give 3 doses. The principle is that adults require a total of 3 vaccinations against tetanus and diphtheria.
  - Give the first 2 doses 1–2 months apart
  - Give the third dose 6–12 months later
  - Give a booster vaccination every 10 years for life; one of the boosters should use Tdap instead of Td booster; if wound is dirty, revaccinate after 5 years

Influenza Vaccine

- Recommended annually for all adults, regardless of age
- Those who will see the greatest benefit from an annual vaccination include:
  - Patients with a history of cardiopulmonary disease, DM, or hemoglobinopathy
  - Residents of a chronic care facility, age 50+
- Pregnant women who will be in their second or third trimester during the influenza season should also receive the vaccine.

Pneumococcal Vaccine

Pneumococcal vaccine is indicated for all adults age ≥65. Additionally, the following individuals should receive the vaccine regardless of age:

- Those with history of sickle-cell disease or splenectomy
- Those with history of cardiopulmonary disease, alcoholism, or cirrhosis
- Alaskan natives and certain Native American populations
- Immunocompromised patients (patients with hematologic malignancies, chronic renal failure, or nephrotic syndrome; HIV-positive patients; or patients receiving immunosuppressive medications)

Revaccination should be performed in healthy patients who received their initial vaccination age <65 and were age <60 at the time of primary vaccination. Patients with a high risk of fatal infection (chronic kidney disease patients, asplenic patients, immunocompromised patients) should be revaccinated 1× after 5 years. No one gets >1 booster shot per lifetime.

Note

Patients must get Pneumovax, meningococcal, and *Haemophilus* vaccines 2 weeks before a splenectomy.

Hepatitis B Vaccine

Hepatitis B vaccine is recommended when there is a history of the following:

- IV drug abuse
- Male homosexuality
- Household or sexual contact with hepatitis B carriers
- Frequent exposure to blood/blood products
- History of chronic liver disease

The hepatitis B vaccine is also recommended for the following individuals:

- All children through age 18
- Those with STIs
- Those who are sexually active but not monogamous
- Workers with occupational exposure to blood
- Prison inmates

Immunity is confirmed serologically.

Hepatitis A Vaccine

The hepatitis A vaccine protects against the virus in >95% of cases. There are 2 types of vaccine, both of which stimulate active immunity against a future infection.

- One contains inactivated hepatitis A virus
- One contains a live but attenuated virus

For the best protection, give the vaccine in 2 doses: initial dose and then a booster 6–12 months later. Protection against hepatitis A begins approximately 2–4 weeks after the initial vaccination.

In the United States, the vaccine is strongly recommended for all children age 12–23 months in an attempt to eradicate the virus nationwide. There are also recommendations that the following populations be vaccinated:

- All children age >1 year
- People whose sexual activity puts them at risk
- People with chronic liver disease
- People who are being treated with clotting factor concentrates
- People who are living in communities where an outbreak is present

Hepatitis A is the most common vaccine-preventable virus acquired during travel, so people traveling to places where the virus is common (Indian subcontinent, Africa, Central America, South America, the Far East, and Eastern Europe) should be vaccinated.

Varicella Vaccine

The varicella vaccine is a live attenuated vaccine recommended for use in all adults who lack a history of childhood infection with varicella virus. Being a live attenuated vaccine, varicella vaccine should not be given to immunocompromised patients, HIV-positive patients when symptomatic or <200 CD4 cells, or pregnant women.

Patients age ≥60 are recommended to receive the varicella zoster (shingles) vaccine, which has been shown to reduce the risk of zoster and its associated pain (post-herpetic neuralgia). It is indicated regardless of whether there is a history of shingles, as it is possible to have a second herpes zoster infection.

Measles, Mumps, Rubella Vaccine

The measles, mumps, rubella (MMR) vaccine is a live attenuated vaccine usually given in childhood. Healthy adults born after 1956 should receive 1 dose of the vaccine. Pregnant women and immunocompromised patients should not be vaccinated. HIV-positive patients who are asymptomatic may receive the vaccine.

Meningococcal Vaccine

The meningococcal vaccine is recommended for everyone at age 11 visit. It is also recommended for young adults living in dormitories or barracks, people exposed to outbreaks, those with asplenia or terminal complement deficiencies, those who travel to endemic regions (traveling to Mecca), and those exposed to *Neisseria meningitidis*.

Human Papillomavirus (HPV) Vaccine

The HPV vaccine is recommended for women age 9–26, regardless of sexual activity. The regimen is in 3 doses: 0, 2, and 6 months.

Do not administer the HPV vaccine in pregnancy.

Herpes Zoster Vaccine

The zoster vaccine is a live vaccine that has been shown to reduce the incidence of shingles by 50%. It has also been shown to reduce the number of cases of post-herpetic neuralgia, as well as the severity and duration of pain/discomfort associated with shingles. The vaccine is, basically, a larger-than-normal dose of the chickenpox vaccine, as both shingles and chickenpox are caused by the same virus, varicella zoster virus (VZV).

The shingles vaccine (Zostavax), a live vaccine given as a single injection, is recommended for adults age ≥60, whether they have already had shingles or not. Some people report a chickenpox-like rash after receiving it. The vaccine should not be given to the following individuals:

- Those with a weakened immune system due to HIV/AIDS or another disease that affects the immune system
- Those who are receiving immune system-suppressing drugs or treatments such as steroids, adalimumab (Humira), infliximab (Remicade), etanercept (Enbrel), radiation or chemotherapy
- Those who have neoplasia, which affects the bone marrow or lymphatic system, such as leukemia or lymphoma

Recombinant zoster vaccine (Shingrix) **(preferred over Zostavax by the CDC)** is a newer vaccine for healthy adults age ≥50 (with no maximum age). It is not indicated for the prevention of primary varicella infection (chickenpox).

Shingrix is given in 2 doses, 2–6 months apart. Side effects include skin rash, joint pain, flu-like symptoms, headaches, and fatigue.

Patients can receive Shingrix even if they have had shingles, have already received Zostavax vaccine, or are not sure if they have ever had chickenpox.

Clinical Recall

In which of the following patients will the vaccination have the greatest benefit?

A. Routine hepatitis A vaccination in a 2-month-old infant

B. Influenza vaccine in a 16-year-old asymptomatic high school student

C. VZV vaccination given to an AIDS patient with CD4 count 100

D. Pneumococcal vaccination given to a 48-year-old male COPD patient

E. HBV vaccination given to a heart failure patient

Answer: D

LIFESTYLE MEDICINE

Alcohol

Physicians should screen for alcohol abuse by using the CAGE questionnaire.

Have you ever felt the need to:	**C**ut down on your drinking?
Have you ever felt:	**A**nnoyed by criticism of your drinking?
Have you ever felt:	**G**uilty about your drinking?
Have you ever taken a morning:	**E**ye opener?

A positive screen is 2 "yes" answers. One "yes" should raise the possibility of alcohol abuse.

Smoking

Smoking is responsible for 1 in every 5 deaths in the United States. Smoking cessation is the most preventable cause of disease. Physicians can take the following steps to assist:

- ASK about smoking at every visit.
- ADVISE all smokers to quit at every visit.
- ATTEMPT to identify those smokers willing to quit.
- ASSIST the patient by setting a quit date (usually within 2 weeks) and using nicotine patches/gum, the oral antidepressant bupropion or varenicline as supportive therapy. Varenicline and bupropion are more effective than patches.
- ARRANGE follow-up. If the quit attempt was successful, then provide positive reinforcement. If it was not successful, then determine why the patient smoked and elicit a recommitment to smoking cessation. Most patients require several attempts before being successful.

Note

Do not use varenicline in patients with a history of psychiatric disease.

Monotherapy treatment for smoking cessation includes nicotine replacement therapy (transdermal nicotine patches, gum, lozenges, inhalers), bupropion, and varenicline.

- Bupropion lowers the seizure threshold so do not use in cases of alcohol abuse.
- Varenicline causes an increased rate of suicidal thoughts, so first screen for depression.

Place a follow-up call 1–2 weeks after quit date. The use of pharmacotherapy doubles the effect of any tobacco cessation intervention.

VIOLENCE AND INJURY

A 27-year-old woman presents to the ED with right-arm pain. When asked how she sustained the injury, she states that she fell down the steps in front of her house. The patient appears anxious and nervous. On physical examination there are various 2 cm wide lacerations on her buttocks.

Injuries are the most common cause of death in those age <65. The role of the physician is to advise patients about safety practices that can prevent injury, e.g., using seat belts, wearing bicycle helmets, and not driving after drinking alcohol.

Identifying women who are at increased risk of physical or sexual abuse is an essential role for a physician. Simply asking them if they have been hit, kicked, or physically hurt can increase identification by >10%.

Clinical Recall

Which of the following is indicated in a 65-year-old male smoker?

A. Digital rectal examination with prostatic specific antigen level

B. Meningococcal vaccination

C. Varicella-zoster vaccination

D. Varicella-zoster vaccination and hepatitis A vaccination

E. Varicella-zoster vaccination and abdominal ultrasound

Answer: E

Endocrinology 2

Learning Objectives

- ❏ List presenting signs and therapeutic approaches to disease of the anterior pituitary, posterior pituitary, thyroid, parathyroid, and adrenal glands
- ❏ Describe disorders that cause hypogonadism or affect the testes
- ❏ Describe disorders of carbohydrate metabolism

DISEASES OF THE PITUITARY GLAND

The pituitary is surrounded by the sphenoid bone and covered by the sellar diaphragm, an extension from the dura mater. It lies in the sella turcica near the hypothalamus underneath the optic chiasm.

The pituitary is divided into 2 lobes:

- Adenohypophysis (anterior lobe) (80% of pituitary)
- Neurohypophysis (posterior lobe) (20%)
  - Stores hormones produced by neurosecretory neurons (supraoptic and paraventricular nuclei) within the hypothalamus
  - Hypothalamus secretes ADH (antidiuretic hormone or vasopressin) and oxytocin

There is a close relationship between the hypothalamus and the pituitary. The hypothalamus regulates the release of hormones from the anterior pituitary by different hypothalamic releasing and inhibiting hormones (hypothalamic–pituitary axis).

The hypothalamus secretes releasing factors for each respective pituitary stimulatory hormone. Each pituitary hormone stimulates release of the active hormone from the final target gland. The active hormones then inhibit release of releasing factors and stimulatory hormones from the hypothalamus and pituitary gland, respectively. This is feedback inhibition, and it leads to a steady state of both respective hormones involved in the axis.

Note

- The posterior lobe does not actually produce hormones.
- It stores and secretes hormones produced by the hypothalamus.

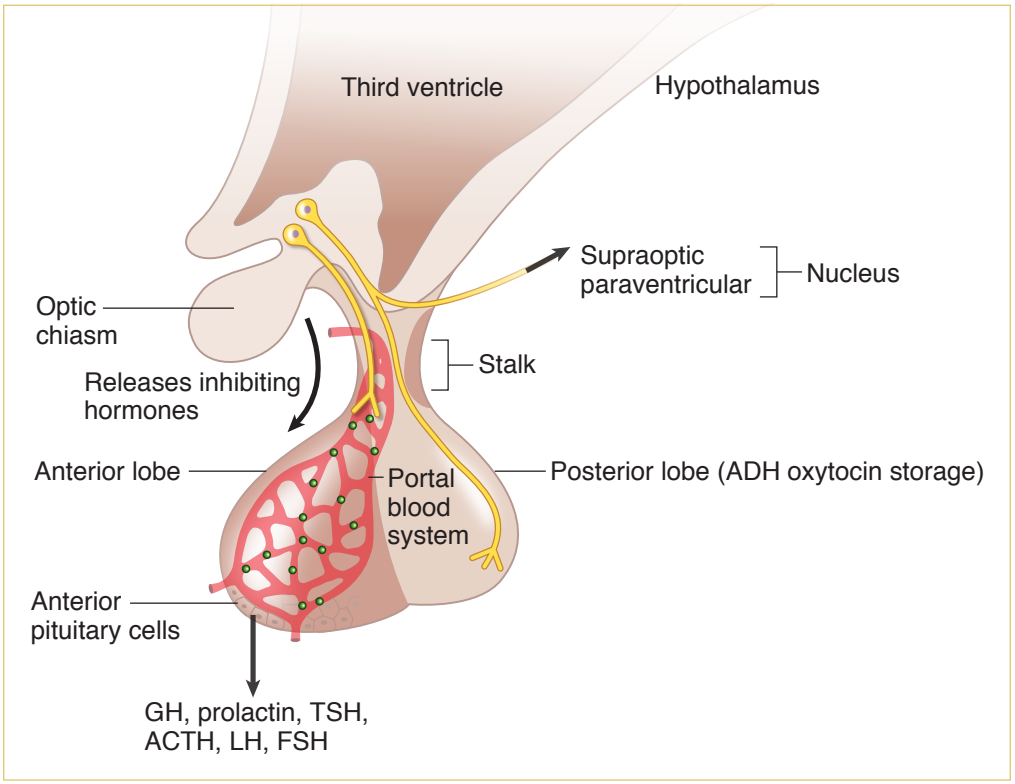


Figure 2-1. Pituitary Gland

Clinically, note the following when diagnosing disease:

- Disease states involving **overproduction of target hormones** lead to **suppressed levels** of pituitary hormones.
- Disease states involving **underproduction of target hormones** lead to **increased levels** of pituitary hormones.

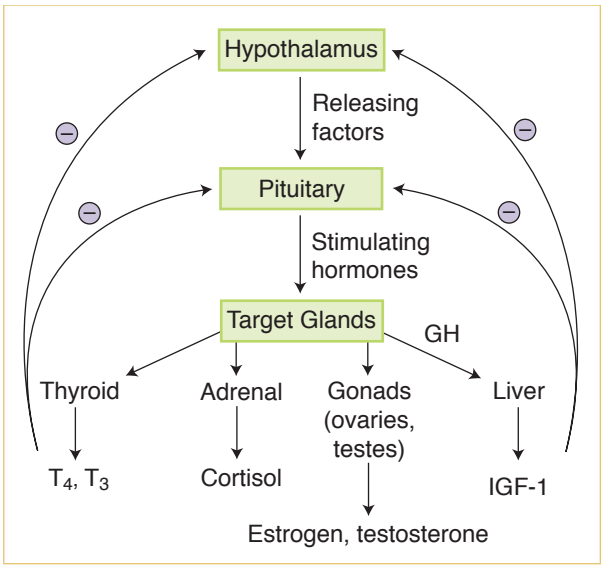


Figure 2-2. Summary of Action

Anterior Pituitary

Syndromes causing excess production of hormones usually arise from benign tumors of a single cell type.

- **Microadenomas** (**more common**) are <1 cm in diameter.
- **Macroadenomas** (less common) are >1 cm in diameter; larger tumors sometimes compress the optic chiasm and cause visual deficits.

The frequency of pituitary adenomas by function is as follows.

- Prolactin: 50–60%
- Growth hormone (GH): 15–20%
- ACTH: 10–15%
- Gonadotroph: 10–15%

Hyperprolactinemia

A 32-year-old woman presents with milk-like discharge from her breasts for the past 4 weeks. She explains that she has not menstruated in 2 months. Physical examination is normal with the exception of galactorrhea.

Excess prolactin secretion (**common in women**) causes the syndrome of galactorrhea-amenorrhea. The amenorrhea appears to be caused by inhibition of hypothalamic release of gonadotropin-releasing hormone (GnRH), with a decrease in luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretion. Prolactin inhibits the LH surge that causes ovulation. The LH/FSH-producing cells are not destroyed, just suppressed.

Note

Gynecomastia, and especially galactorrhea, are much rarer in men than is hyperprolactinemia. The most common presenting symptoms of hyperprolactinemia in men are erectile dysfunction and decreased libido.

Hyperprolactinemia can be caused by the following conditions:

- Natural physiologic states such as pregnancy, early nursing, hypoglycemia, seizure, exercise, stress, sleep, cirrhosis, nipple stimulation, and chronic renal failure (due to PRL clearance)
- Pituitary adenomas: autonomous production of prolactin ("prolactinomas") are the most common functioning pituitary adenomas (60% of all pituitary tumors)
  - In **women**, usually microadenomas
  - In **men**, usually macroadenomas (usually present with visual field deficits, obstruction of pituitary stalk, and increased prolactin release by blocking dopamine transport from hypothalamus (stalk effect)
- Other tumors such as craniopharyngioma/meningioma/dysgerminoma; empty sella; and trauma
- Decreased inhibitory action of dopamine, seen in dopamine-blocking agents (phenothiazines, metoclopramide) and dopamine-depleting agents (α-methyldopa, reserpine)
- Tricyclic antidepressants, narcotics, cocaine, CCBs, protease inhibitors, SSRIs, risperidone
- Stimuli which overcome the normal dopamine inhibition, e.g., primary hypothyroidism (causing increased thyrotropin-releasing hormone [TRH]) and subsequent increased prolactin release)

Note

Always check TSH in patients with elevated prolactin.

Clinical Presentation.

- Galactorrhea (mostly women)
- Menstrual abnormalities amenorrhea/oligomenorrhea (results in earlier detection in women; thus, microadenomas are more common in women)
- Osteopenia and osteoporosis (in chronic cases)
- Infertility
- Gynecomastia
- Hypogonadism, erectile dysfunction, decreased libido (men)

Diagnosis. To diagnose, first exclude pregnancy, lactation, hypothyroidism, and medication. Prolactinomas may co-secrete GH.

- Prolactin level >100 ng/mL suggests probable pituitary adenoma
- Prolactin level should be commensurate with tumor size
  - Prolactin 100 ng/mL correlates with tumor ~1 cm
  - Prolactin 200 ng/mL correlates with tumor ~2 cm
- Prolactin level influenced by drugs and other nonprolactinoma conditions are usually <150 ng/mL. If someone is on a psychotropic agent and prolactin >150 ng/mL, do a brain MRI.

Treatment. Dopamine normally inhibits prolactin release.

- Treat initially with dopamine-agonists (cabergoline [**preferred**] or bromocriptine), which will reduce prolactin level to <10% of pretreatment level (90% success rate)
  - Dopamine-agonists are always **first line**, even when there are mass effects compressing the optic chiasm or invasion of cavernous sinus or vessels.
  - Cabergoline has fewer side effects than bromocriptine, so is preferred for galactorrhea.
- If no response to cabergoline or bromocriptine, or if significant compressive neurologic effects, consider surgery
  - Surgery is more effective for microadenomas than macroadenomas.
  - Only 30% of macroadenomas can be successfully resected, with long-term recurrence >50%.
- If no response to drug therapy or surgery, consider radiation therapy

Clinical Recall

Which of the following options is most appropriate in the treatment of prolactinoma?

A. Somatostatin

B. Surgical resection

C. Transsphenoidal resection

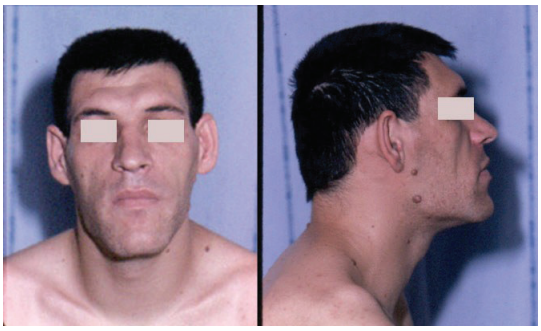
D. Radiation therapy

E. Cabergoline

Answer: E

Acromegaly

Acromegaly (called gigantism in children) is a syndrome of excessive secretion of GH. It is an insidious, chronic debilitating disease associated with bony and soft tissue overgrowth, and increased mortality.



Wikimedia, Philippe Chanson and Sylvie Salenave

Figure 2-3. Acromegaly Facial Features

Note

A basal, fasting, morning PRL >100–200 mg/L (normal <20 mg/L) in a nonpregnant woman indicates a need for a pituitary MRI.

Acromegaly is caused by a pituitary adenoma (usually macroadenoma in 75% of the cases that produce GH). Rarely, ectopic tumors can produce growth hormone-releasing hormone (GHRH) and cause this syndrome. Less than 1% of cases are malignant. GH is produced by 20% of pituitary tumors.

Clinical Findings. GH excess occurs most frequently around decades 3–5. The following symptoms may be seen.

- Enlargement of hands/feet, coarsening of facial features, and thickened skin folds; increase in shoe/hat/glove/ ring size
- Enlarged nose and mandible (prognathism and separation of teeth), sometimes causing underbite
- Deeper voice
- Increased sweating
- Obstructive sleep apnea
- Enlarged internal organs, including heart, lung, spleen, liver, and kidneys
- Interstitial edema, osteoarthritis, and entrapment neuropathy (carpal tunnel syndrome)
- Menstrual problems (**common**) due to co-secretion of prolactin by GH-producing tumor
- Cardiac anomalies (10–20%) such as hypertension, arrhythmia, hypertrophic cardiomyopathy, and accelerated atherosclerosis
- Metabolic changes, i.e., impaired glucose tolerance (80%) and diabetes (13–20%)
- Hypertension (35%)
- Headaches and visual field loss

Note

The most common cause of death in acromegaly is cardiovascular mortality.

Diagnosis. Patients with acromegaly have symptoms for ~9 years before the diagnosis is made. Measurement of insulin-like growth factor (IGF) or somatomedin correlates with disease activity.

- Significantly elevated IGF-1 (**best initial test**)
- Confirmatory test is GH measurement (after 100 g of glucose is given orally)
  - If GH remains high (>5 ng/mL), it is positive and suggests acromegaly.
  - Normally, glucose load should completely suppress levels of GH.
- MRI (**preferred**; highly diagnostic) and CT to localize the tumor, but only after GH excess is documented biochemically

Treatment. The goals of treatment are to decrease GH levels to normal, stabilize/decrease tumor size, and preserve normal pituitary function (hypopituitarism is a side effect in 10–20% of cases).

- Transsphenoidal surgery provides a rapid response
- Somatostatin analogues (**drugs of choice**)
  - Octreotide (**preferred**) and lanreotide reduce GH (70% success rate) and cause partial tumor regression (20–50% success rate).
  - Main side effect is cholestasis, leading to cholecystitis

- If surgery is not curative, dopamine-agonists such as bromocriptine and cabergoline (10% success rate)
- Pegvisomant (**second-line**), a GH analogue that antagonizes endogenic GH by blocking peripheral GH binding to its receptor in the liver
- If surgery and drug therapy are not curative, radiotherapy can slow resolution of disease and hypopituitarism (20% success rate)

Complications of acromegaly include pressure of the tumor on the surrounding structures or invasion of the tumor into the brain or sinuses; cardiac failure (**most common cause of death**), DM, cord compression, and visual field defects.

Hypopituitarism

Hypopituitarism is partial/complete loss of anterior function resulting from any lesion that destroys the pituitary or hypothalamus or interferes with the delivery of releasing and inhibiting factors to the anterior hypothalamus. GH and gonadotropins (FSH, LH) are typically lost early.

Causes include:

- Large pituitary tumors or cysts
- Hypothalamic tumors (craniopharyngiomas, meningiomas, gliomas)
- Pituitary adenomas (**most common cause of panhypopituitarism**); the mass compresses the gland, causing pressure, trauma, and necrosis
- Pituitary apoplexy (**medical emergency**), a syndrome associated with acute hemorrhagic infarction of a preexisting pituitary adenoma; symptoms include severe headache, nausea/vomiting, and depression of consciousness
- Inflammatory disease
  - Granulomatous disease (sarcoidosis, TB, syphilis), eosinophilic granuloma, and autoimmune lymphocytic hypophysitis (usually associated with other autoimmune diseases such as Hashimoto thyroiditis and gastric atrophy)
  - Trauma, radiation, surgery, infections, and hypoxia, which may damage both the pituitary and hypothalamus
  - Vascular disease such as Sheehan postpartum necrosis (initial sign is the inability to lactate) and infiltrative diseases, e.g., hemochromatosis and amyloidosis
  - Stroke, which can cause central diabetes insipidus (DI) due to damage of hypothalamus and/or posterior pituitary

Clinical Findings. The following hormones appear in the **order in which they are lost in hypopituitarism**.

- Gonadotropin deficiency (LH and FSH) can occur in women and lead to amenorrhea, genital atrophy, infertility, decreased libido, and loss of axillary and pubic hair.
- In men, decreased LH and FSH results in impotence, testicular atrophy, infertility, decreased libido, and loss of axillary and pubic hair.

- GH deficiency occurs next.
  - Not clinically detectable in adults, though it may manifest as fine wrinkles and increased sensitivity to insulin (hypoglycemia)
  - Causes an asymptomatic increase in lipid levels and a decrease in muscle, bone, and heart mass
  - May accelerate atherosclerosis
  - Increases visceral obesity
  - In children, results in growth failure and short stature
- TSH deficiency results in hypothyroidism with fatigue, weakness, hyperlipidemia, cold intolerance, and puffy skin without goiter.
- Adrenocorticotropin hormone (ACTH) deficiency occurs last. It causes secondary adrenal insufficiency caused by pituitary disease (and does not result in the salt-wasting, hyperpigmentation, hyperkalemia, and death associated with aldosterone deficiency)
- Decreased cortisol, which results in fatigue, reduced appetite/weight loss, decreased skin/nipple pigment, and decreased response to stress (as well as fever, hypoglycemia, hypotension, and hyponatremia).

Electrolyte changes like hyperkalemia and salt loss are minimal in secondary adrenal insufficiency because aldosterone production is mainly dependent on the renin-angiotensin system.

Diagnosis. The first step in diagnosing pituitary insufficiency is to measure GH, TSH, LH, and IGF-1.

Note

Random GH and IGF levels are not sensitive enough to diagnose GH deficiency, which is why a provocative test is used.

- To diagnose **GH deficiency**, the most reliable stimulus for GH secretion is insulin-induced hypoglycemia.
  - After injecting 0.1 μ/kg of regular insulin, blood glucose declines to <40 mg/dL (in normal conditions that will stimulate GH levels to >10 mg/L and exclude GH deficiency).
  - Arginine infusion can also stimulate GH release. Measure GH after infusing arginine. This is less dangerous because it does not cause hypoglycemia.
- To diagnose **ACTH deficiency**, basal cortisol levels may be normal (the problem could be only in response to stress). Insulin tolerance test is diagnostic (give 0.05–0.1 U/kg of regular insulin and measure serum cortisol); plasma cortisol should increase to >19 mg/dL. Metyrapone tests for decreased ACTH production.
  - Metyrapone blocks cortisol production, which should increase ACTH. Failure of ACTH to increase after metyrapone administration would indicate pituitary insufficiency.
  - Cosyntropin (ACTH) stimulation may give abnormally low cortisol output if pituitary insufficiency has led to adrenal atrophy.
- To diagnose **gonadotropin deficiency**
  - LH, FSH, and estrogen (women)
  - LH, FSH, and testosterone (men)
- To diagnose **TSH deficiency**, measure serum thyroxine (T4) and free triiodothyronine (T3), which are low, with a normal/low TSH.

Treatment. Treat the underlying cause. Multiple hormones must be replaced, the most important of which is cortisol.

- Cortisol must be given before T4; otherwise an adrenal crisis can occur.
- Cosyntropin stimulation test must be done before T4 to rule out adrenal insufficiency if secondary hypothyroidism is suspected (risk factors include radiation to the head, sarcoidosis, hemochromatosis, Sheehan syndrome, or TSH that is not elevated).

Empty Sella Syndrome (ESS)

ESS is in the differential diagnosis of enlarged sella caused by pituitary tumors. In ESS, the sella has no bony erosion. It is caused by herniation of the suprasellar subarachnoid space through an incomplete diaphragma sellae.

The syndrome can be primary (idiopathic) and is also associated with head trauma and radiation therapy.

Most patients are obese, multiparous women. Symptoms include:

- Headaches (**common**)
- Hypertension (30% of patients)
- Endocrine symptoms are absent.
- No pituitary gland is visible on CT or MRI.

Treatment is reassurance.

Note

- In **primary hypothyroidism**, TSH will always be elevated due to loss of negative feedback inhibition.
- In **secondary hypothyroidism**, TSH can be normal.

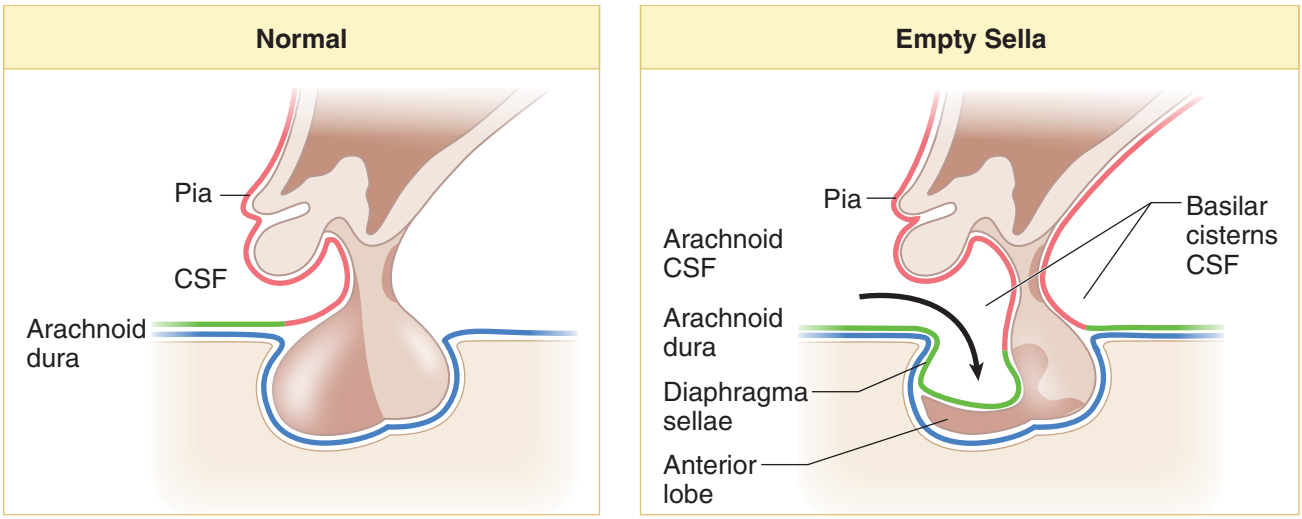


Figure 2-4. Empty Sella Syndrome

Clinical Recall

What is the best initial test to diagnose acromegaly?

A. 100 g oral glucose tolerance test

B. Insulin-like growth factor-1 levels

C. MRI of the brain

D. Pituitary biopsy

E. Adrenal venous sampling

Answer: B

Posterior Pituitary

Vasopressin (or ADH) and oxytocin are synthesized in neurons of the supraoptic and paraventricular nuclei in the hypothalamus, then transported to the posterior pituitary lobe to be released into the circulatory system.

- ADH deficiency will cause DI.
- ADH excess will cause syndrome of inappropriate secretion of ADH (SIADH).

Diabetes Insipidus

DI often starts in childhood or early adult life. Men > women.

- **Central DI** is a disorder of the neurohypophyseal system caused by partial or total deficiency of ADH. It leads to excessive, dilute urine and increased thirst associated with hypernatremia.
  - Causes include neoplastic or infiltrative lesions of the hypothalamus or pituitary (60% also have partial or complete loss of anterior pituitary function); in the hypothalamus these lesions can be secondary to adenoma, craniopharyngioma, etc.; in the pituitary gland, adenoma, leukemia, or sarcoid histiocytosis can lead to DI
  - Other causes include pituitary or hypothalamic surgery, radiotherapy, severe head injuries, anoxia, hypertension, meningitis
  - Idiopathic DI starts in childhood
  - Encephalitis, TB, and syphilis may affect the pituitary as well
- **Nephrogenic** DI is caused by renal resistance to the action of vasopressin. It can be idiopathic or it can be secondary to hypercalcemia, hypokalemia, sickle cell disease, amyloidosis, myeloma, pyelonephritis, sarcoidosis, or Sjögren syndrome.
  - Causes include drugs (lithium, demeclocycline, colchicine)

Clinical Findings. Clinical findings of DI include polyuria, excessive thirst, polydipsia (16–20 L/d), hypernatremia with high serum osmolarity and coexisting low urine osmolarity and urine specific gravity <1.010. Nocturia is expected.

Hypertonicity is not usually present if the patient has an intact thirst mechanism and can increase water intake to keep up with urinary loss.

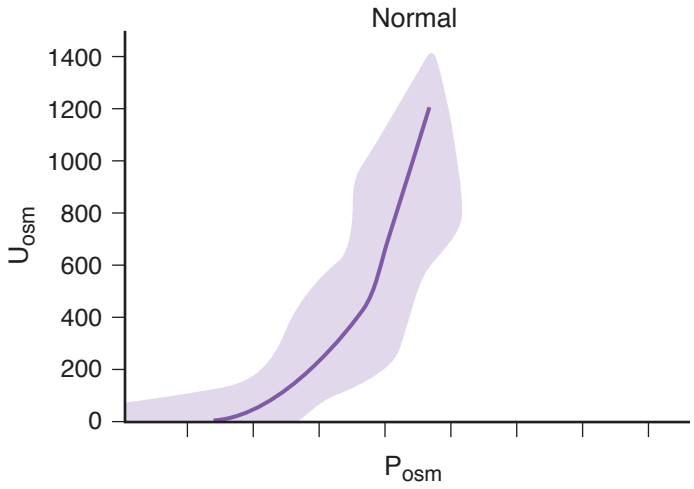


Figure 2-5. P_{osm} versus U_{osm} during Dehydration in Normal Subjects

Diagnosis. The water deprivation test compares U_{osm} after dehydration versus U_{osm} after vasopressin.

- In a healthy person, the response to fluid restriction is decreased urine volume and increased urine osmolality.
- In a person with DI, urine volume remains increased and urine osmolality remains low (<200 mOsm/kg H2O) despite volume depletion.
- ADH will be decreased in central DI and increased in nephrogenic DI. If a patient falls to the right of the shaded area, the diagnosis is DI.

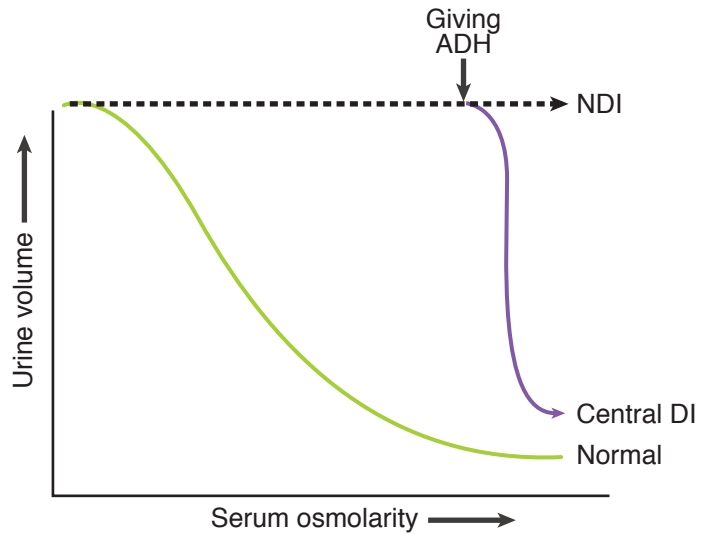


Figure 2-6. Water Restriction Test

The differential diagnosis of DI includes primary disorders of water intake (psychogenic polydipsia, drug-induced polydipsia from chlorpromazine, anticholinergic drugs, or thioridazine) and hypothalamic diseases.

Treatment.

- Hormone replacement with vasopressin subcutaneously or desmopressin subcutaneously, orally, or intranasally
- Drugs to stimulate the secretion of ADH or increase release (chlorpropamide, clofibrate, or carbamazepine)
- HCTZ or amiloride (for nephrogenic DI) to enhance the reabsorption of fluid from proximal tubule
- Chlorthalidone
- Correction of any calcium and/or potassium abnormalities

Syndromes associated with ADH excess involve a mechanism of defense against hypovolemia or hypotension. This includes adrenal insufficiency, excessive fluid loss, fluid deprivation, and probably positive-pressure respiration.

Excessive release of ADH from the neurohypophysis is associated with drugs or diseases (SIADH).

Syndrome of Inappropriate Antidiuretic Hormone

Note

Syndromes associated with an excess of ADH involve a mechanism of defense against hypovolemia or hypotension such as adrenal insufficiency, excessive fluid loss, fluid deprivation, and probably positive-pressure respiration. Excessive release of ADH from the neurohypophysis is associated with drugs or diseases e.g., SIADH.

Causes include:

- Malignancy, e.g., small cell carcinoma, carcinoma of the pancreas, ectopic ADH secretion
- Nonmalignant pulmonary disease, e.g., TB, pneumonia, lung abscess
- CNS disorder, e.g., head injury, cerebral vascular accident, encephalitis
- Drugs, e.g., chlorpropamide, clofibrate, vincristine, vinblastine, cyclophosphamide

In general, increased ADH causes water retention and extracellular fluid volume expansion without edema or hypertension, owing to natriuresis. Symptoms include:

- Hyponatremia (**key feature in SIADH**) as a result of water retention and sodium loss
  - Concentrated urine (U_{osm} >300 mOsm)
  - If hyponatremia is severe (sodium <120 mOsm) or acute in onset, symptoms of cerebral edema will be seen: irritability, confusion, seizures, coma
- No signs of edema or dehydration

Diagnosis. Lab findings in SIADH include:

- Hyponatremia <130 mEq/L (possible causes include hypothyroidism and adrenal insufficiency)
- P_{osm} <270 mOsm/kg
- Urine sodium concentration >20 mEq/L (inappropriate natriuresis)
- Urine osmolality >300 mOsm/kg
- Euvolemia (normal volume) on physical exam

- Suppression of renin–angiotensin system
- No equal concentration of atrial natriuretic peptide
- Low blood urea nitrate (BUN), low creatinine, low serum uric acid, and low albumin

Management. Treat underlying causes.

- Restrict fluid to 800–1,000 mL/d to increase serum sodium
- For **chronic SIADH**: loop diuretics and oral salt tablets or demeclocycline, which inhibits ADH action at the collecting duct [V2])
- For **moderate/severe** SIADH: V2 receptor blockers conivaptan and tolvaptan
- For **severe symptoms** (severe confusion, convulsions, coma): IV hypertonic saline (3%) 200–300 mL in 3–4 h (if acute, increase by 2.0–4.0 mEq/L)

Never correct sodium >10 mEq/L/24 hrs, which could lead to osmotic demyelination syndrome (central pontine myelinolysis). If correction has been too rapid, give desmopressin and IV 5% dextrose in water.

Clinical Recall

Which of the following lab findings is suggestive of central DI?

A. Increased serum osmolarity, decreased urine osmolarity, decreased ADH
B. Decreased serum osmolarity, increased urine osmolarity, increased ADH
C. Increased serum osmolarity, decreased urine osmolarity, increased ADH
D. Increased serum osmolarity, increased urine osmolarity, increased ADH
E. Decreased serum osmolarity, decreased urine osmolarity, decreased ADH

Answer: A

DISEASES OF THE THYROID GLAND

The normal function of the thyroid gland is directed toward the secretion of L-thyroxine (T4) and L-3,5,5′-triiodothyronine (T3), which influence a diversity of metabolic processes.

Diseases of the thyroid can be quantitative or qualitative alterations in hormone secretion, enlargement of thyroid (goiter), or both.

- Insufficient hormone secretion will lead to **hypothyroidism**.
- Excess hormone secretion will lead to **hyperthyroidism**.
- Generalized enlargement can be associated with increased, normal, or decreased function of the gland, depending on the underlying cause.
- Focal enlargement of the thyroid can be associated with tumors (benign or malignant).

Clinical Pearl

Always check **free** T4 to assess thyroid function.

The most sensitive test in thyroid diseases is the TSH. If TSH is normal, then the patient is euthyroid.

Total T4 and T3, however, does not always reflect actual thyroid function.

- **Increased TBG levels are seen in pregnancy** and the use of oral contraceptives. Total T4 will increase but free or active T4 level will be normal.
- **Decreased TBG levels** are seen in nephrotic syndrome and the use of androgens. Total T4 will decrease but free or active T4 will be normal, with the patient being euthyroid.

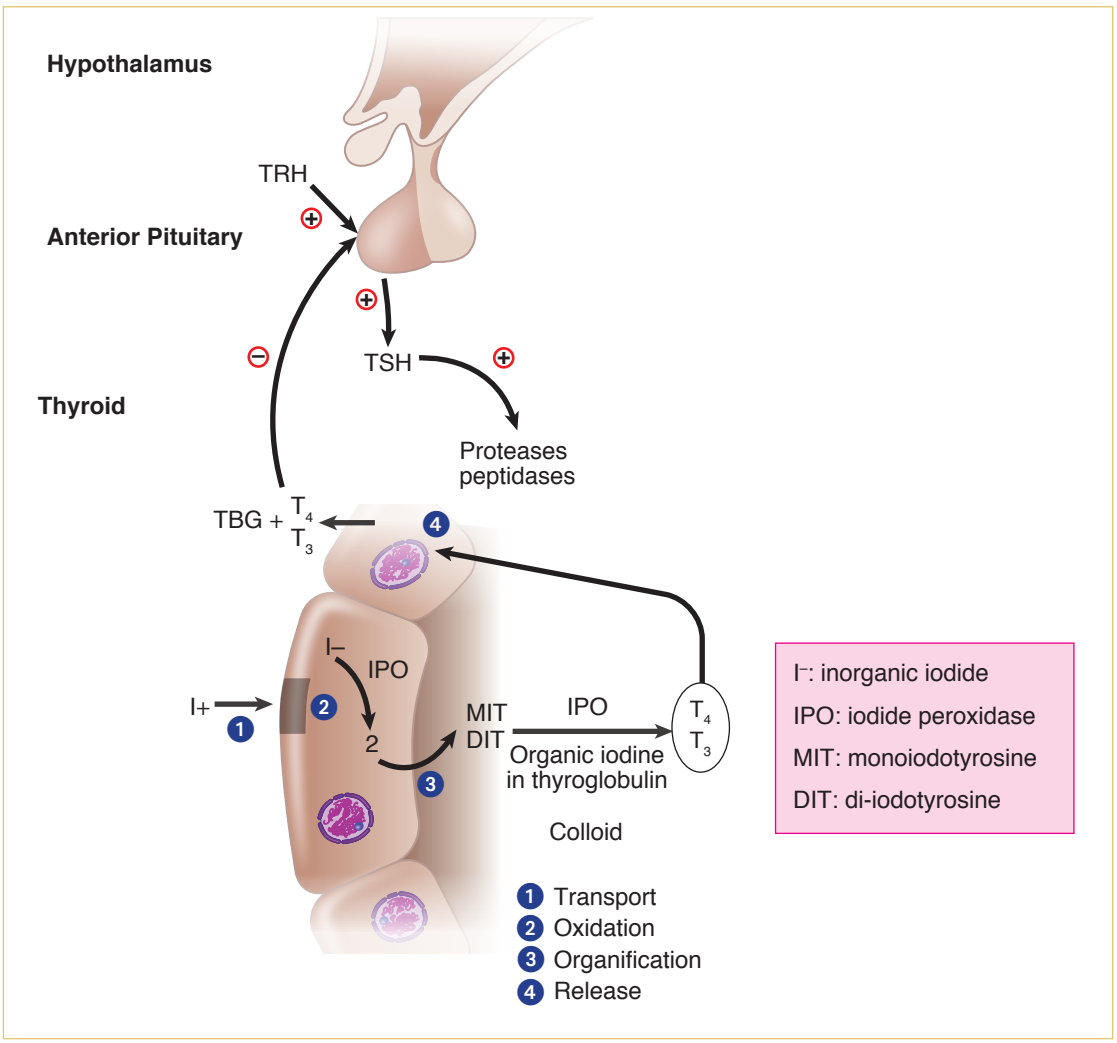


Figure 2-7. Pathways for Synthesis and Secretion of Thyroid Hormones

RAIU (thyroid-reactive iodine uptake) varies directly with the functional state of the thyroid. After 24 hours, normal uptake is 5–30% of administered dose.

- RAIU is **increased** in Graves disease and toxic nodule.
- RAIU is **decreased** in thyroiditis and surreptitious ingestion of thyroid hormone.

Table 2-1. Evaluating Thyroid Function

Thyroid Hormones and TSH	RAI Uptake Scan	Diagnosis
• Decreased TSH • Free increased T_4; increased T_3	Increased RAIU	De novo synthesis of hormone (primary hyperthyroidism)
• Decreased TSH • Free increased T_4; increased T_3	Decreased RAIU	Factitious hyperthyroidism or inflammation/destruction of the gland releasing preformed hormone into the circulation (subacute thyroiditis)
• Decreased TSH • Free decreased T_4; decreased T_3	Decreased RAIU	Secondary or tertiary hypothyroidism

Other tests include antimicrosomal and antithyroglobulin antibodies, which are detected in Hashimoto thyroiditis. In Graves disease, thyroid-stimulating immunoglobulin (TSI) is found. Serum thyroglobulin concentration can be used to assess the adequacy of treatment and follow-up of thyroid cancer, and to confirm the diagnosis of thyrotoxicosis factitia.

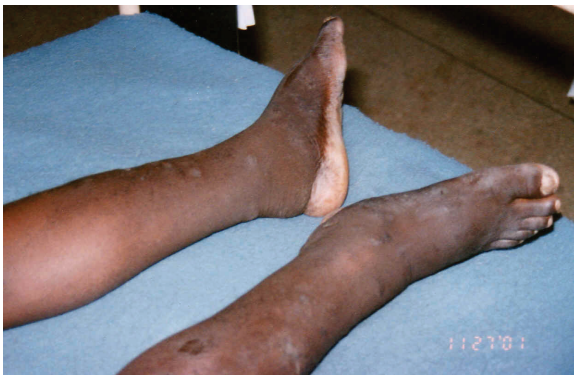
Note

Factitious use of thyroid hormone will suppress thyroglobulin levels.

Hyperthyroidism (Thyrotoxicosis)

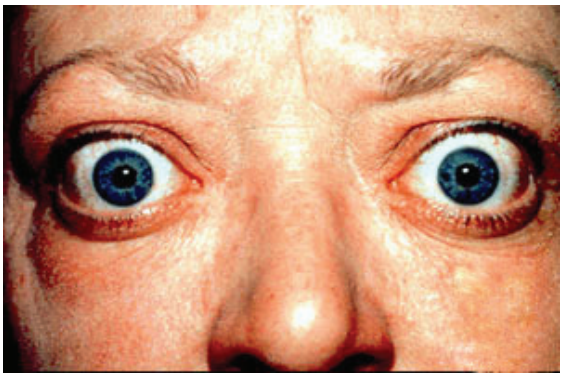
Graves disease (toxic diffuse goiter) is the **most common cause** of hyperthyroidism. Graves is an autoimmune disorder which causes the production of antibodies (TSI). Autoantibodies form and bind to the TSH receptor in thyroid cell membranes, stimulating the thyroid to hypersecrete T4 and T3.

- Commonly affects patients age <50
- Women > men
- Significant genetic component, i.e., a person is more likely to be affected if they have family member with the disease
- Commonly triggered by stress, infection, and pregnancy
- Risk factors include having another autoimmune disease such as type 1 diabetes or pernicious anemia and smoking



Courtesy of Tom D. Thacher, MD

Figure 2-8. Pretibial Myxedema



Wikimedia, Jonathan Trobe, MD/University of Michigan Kellogg Eye Center

Figure 2-9. Proptosis and Lid Retraction

Note

For treatment purposes, it is important to distinguish **primary hyperthyroidism** (Graves disease or toxic adenoma) from **thyroiditis**.

Note

- Because of the high relapse rate (>50%) associated with antithyroid treatment, many clinicians prefer to use radioactive iodine as first-line therapy. Patients currently taking antithyroid drugs must discontinue the medication at least 2 days prior to taking the radiopharmaceutical, since pretreatment with antithyroid drugs reduces the cure rate of radioiodine therapy in hyperthyroid diseases.
- With radioactive iodine, the desired result is hypothyroidism due to destruction of the gland, which usually occurs 2–3 months post-administration, after which hormone replacement treatment is indicated.

Clinical Findings. Graves is associated clinically with diffuse painless enlargement of the thyroid. Additionally:

- Nervous symptoms (younger patients)
- Cardiovascular and myopathic symptoms (older patients)
- Atrial fibrillation
- Emotional lability, inability to sleep, tremors
- Frequent bowel movements
- Excessive sweating and heat intolerance
- Weight loss (despite increased appetite) and loss of strength
- Proximal muscle weakness (prominent symptom in many patients, and the primary reason why they see a physician)
- Dyspnea, palpitations, angina, and possible cardiac failure
- Warm and moist skin
- Palmar erythema, along with fine and silky hair in hyperthyroidism
- Ocular signs such as staring, infrequent blinking, and lid lag
- Menstrual irregularity such as oligomenorrhea
- Osteoporosis and hypercalcemia, as a result of increases in osteoclast activity
- Dermopathy (rare but hallmark sign)
- Proptosis (protrusion of the eyes), pretibial myxedema (specific to Graves)

Diagnosis of Graves is made on history and physical exam. Lab studies include the following:

- Decreased TSH (but elevated TSH in secondary hyperthyroidism)
- High serum free T4 and T3
- Elevated RAIU (but decreased RAIU in subacute thyroiditis and factitious hyperthyroidism)
- Elevated TSI, antithyroglobulin, and antimicrosomal antibodies

Treatment of Graves is relief of symptoms and correction of the thyrotoxic state.

- Beta-adrenergic blockade (propranolol) for adrenergic hyperfunction
- Anti-thyroid medication (methimazole (**preferred**) or propylthiouracil) for high thyroid levels (blocks the synthesis of thyroid hormones and/or by treatment with radioactive iodine)
  - **Methimazole**: long half-life, few side effects; taken 1×/day (often given before radioactive iodine treatment)
  - **Propylthiouracil**: severe side effects (potential liver damage); taken 2–3×/day (use only when methimazole is not appropriate)
- Radioactive iodine (**most commonly used 'permanent' treatment**): indications for its use (overusing antithyroid agents alone) include large thyroid gland; multiple symptoms of thyrotoxicosis; elevated thyroxine; and high titers of TSI
- Subtotal thyroidectomy (and rarely, total thyroidectomy), only in pregnancy (second trimester), in children, and in cases when the thyroid is so large that there are compressive symptoms

To monitor response to treatment, check free T4 and T3—not TSH—because it will be suppressed for a very long time and is not a reliable marker of treatment response.

Other causes of hyperthyroidism include:

- Hyperfunctioning adenoma (toxic adenoma)
- Toxic multinodular goiter (Plummer disease, a non-autoimmune disease of the elderly associated commonly with arrhythmia and CHF)
- Simple goiter
- Subacute thyroiditis (painful) or by lymphocytic thyroiditis (painless, postpartum), which can cause transient hyperthyroidism
- Drugs such as amiodarone, alpha interferon, and lithium, which can induce thyrotoxicosis
- Excess iodine (as with expectorants or an iodine-containing contrast agent for imaging)
- Extrathyroid source of hormones, i.e., thyrotoxicosis factitia and ectopic thyroid tissue (struma ovarii, functioning follicular carcinoma)
- Excess production of TSH (secondary hyperthyroidism) (rare)

Thyroid Storm

Thyroid storm is an extreme form of thyrotoxicosis, and an **endocrine emergency**. It is precipitated by stress, infection, surgery, or trauma. It manifests with extreme irritability, delirium, coma, tachycardia, restlessness, vomiting, jaundice, diarrhea, hypertension, dehydration, and high fever.

Treatment is supportive therapy with saline and glucose hydration, glucocorticoids, and oxygen cooling blanket. Therapy for hyperthyroidism is also used:

- First, give propylthiouracil.
- Next, give iodine to inhibit hormone release.
- Follow with adrenergic antagonists (e.g., β-adrenergic blockers).

Clinical Correlate

For years propylthiouracil was the drug of choice for Graves during pregnancy, because it causes fewer severe birth defects than methimazole. However, after it caused a few cases of liver damage, experts now give propylthiouracil during the first trimester only. Use methimazole after the first trimester. For the same reasons, use methimazole for nursing mothers. Both drugs can cause agranulocytosis.

- Finally, give dexamethasone to provide adrenal support.
- Stop the antithyroid drugs 1–2 weeks before and after the RAI treatment, as they block the uptake of the radioactive iodine.

Subacute Thyroiditis

Thyroiditis includes disorders of different etiologies characterized by inflammation of the thyroid. Each has a different clinical course and can be associated at one time or another with euthyroid, thyrotoxic, or hypothyroid state.

Subacute thyroiditis, most likely viral in origin, includes granulomatous, giant cell, or de Quervain thyroiditis. It is commonly seen in decades 4 and 5.

- Follows upper respiratory infection symptoms, e.g., malaise, fever, pain over the thyroid, and pain referred to the lower jaw, ears, neck, or arms
- Thyroid gland is enlarged and firm
- Lab findings include elevated erythrocyte sedimentation rate, decreased radioactive iodine uptake, initial elevation in T_4 and T_3 (due to leak of hormone from the gland) followed by hypothyroidism as the hormone is depleted
- Differential diagnosis includes mostly Graves disease

Treatment is symptomatic with NSAIDs, prednisone, and propranolol. The disorder may smolder for months but eventually subsides with return to normal function.

Clinical Pearl

When large quantities of iodide are ingested by patients with hyperthyroidism, the result is thyroid hormone suppression (**Wolff-Chaikoff effect**).

Hypothyroidism

The far majority of hypothyroidism has a thyroid etiology (primary). Causes include:

- Chronic lymphocytic thyroiditis (Hashimoto disease) (**most common cause of goitrous hypothyroidism**; associated with antimicrosomal antibodies) is a chronic inflammatory process of the thyroid with lymphocytic infiltration of the gland.
  - Commonly seen in middle-aged women; in children, is the most common cause of sporadic goiter
  - Most likely caused by autoimmune factors, as evidenced by lymphocytic infiltration, increased immunoglobulin, and antibodies against components of thyroid tissue (antithyroglobulin Abs)
  - Hallmark feature is a goiter that is painless; rubbery; not always symmetric; diagnosis is suggested by finding a firm, nontoxic goiter on examination
  - Lab findings include metabolically normal values in early stages, then increased TSH and decreased T3 and T4; high titers of antithyroid antibodies, namely antimicrosomal antibodies, are found, as are antithyroperoxidase antibodies
- Postablative surgery or radioactive iodine, heritable biosynthetic defects, and iodine deficiency
- Drugs such as lithium and acetylsalicylic acid
- Suprathyroid causes of hypothyroidism include pituitary induced (secondary hypothyroidism) or hypothalamic induced (tertiary hypothyroidism)

Clinical Correlate

Amiodarone is an antiarrhythmic drug used to treat ventricular and supraventricular tachyarrhythmia.

- Structurally similar to T4 and contains approximately 40% iodine
- Highly lipid-soluble and concentrated in the adipose tissue, muscle, liver, lung, and thyroid gland
- Has a high elimination half-life (50–100 days) so total body iodine stores can remain increased for up to 9 months after drug is discontinued

- Amiodarone, interferon, and sulfonamides
  - Thyroid abnormalities are seen in up to 20% of patients receiving long-term amiodarone treatment. (However, other research has shown that with lower doses of amiodarone, incidence of thyroid dysfunction is around 4%.) The effects range from abnormal thyroid function test findings (without clinical hyper- or hypothyroidism) to overt thyroid dysfunction, which may be amiodarone-induced thyrotoxicosis or amiodarone-induced hypothyroidism (both can develop in apparently normal thyroid glands or in glands with preexisting abnormalities).
  - Amiodarone-induced thyrotoxicosis **type 1** occurs in patients with underlying thyroid pathology, e.g., autonomous nodular goiter or Graves (treatment is antithyroid therapy), while **type 2** is a result of amiodarone causing a subacute thyroiditis, with release of preformed thyroid hormones into the circulation (treatment is glucocorticoids).
  - Amiodarone-induced hypothyroidism is due to inhibition of peripheral conversion of T4 to T3.

Clinical Findings.

- In the **newborn**, cretinism (in 1/5,000 neonates) and juvenile hypothyroidism; persistent physiologic jaundice, hoarse cry, constipation, somnolence, and feeding problems
- In **later months**, delayed milestones and dwarfism, coarse features, protruding tongue, broad flat nose, widely set eyes, sparse hair, dry skin, protuberant abdomen, potbelly with umbilical hernia, impaired mental development, retarded bone age, and delayed dentition
- In the **adult**, there are stages:
  - **Early stages** may include lethargy; constipation; cold intolerance; stiffness/cramping of muscles; carpal tunnel syndrome; menorrhagia
  - **Later stages** may include slowing intellectual and motor activity; decreased appetite; weight gain, dry hair/skin, deeper, hoarse voice; deafness; elevated cholesterol and slow, deep tendon reflexes; hyponatremia and anemia
  - **Ultimately**, myxedema (expressionless face, sparse hair, periorbital puffiness, large tongue, and pale, cool skin that feels rough and doughy)
- Hypercholesterolemia and diastolic hypertension (increase in vascular resistance) (**common**)
- Myositis (**very common**) (everyone with myopathy should have TSH checked, even if on a statin)
- Weakness, cramps, and myalgias
- Elevated serum CK
- Increased CPK, AST, hyponatremia, and LDH (associated with 10% pernicious anemia)

Diagnosis of hypothyroidism is made with symptoms and physical findings. Lab tests confirm diagnosis.

Note

- In primary hypothyroidism, TSH will always be elevated due to loss of negative feedback inhibition.
- If TSH is normal with low T4 or T3, that is **secondary** (pituitary-induced) hypothyroidism, not primary!

Table 2-2. Confirmation of Hypothyroid Diagnosis

Primary Hypothyroidism	Secondary or Tertiary Hypothyroidism
Increased TSH	Normal or decreased TSH
Decreased T_4 and FT_4	Decreased T_4 and FT_4
Mildly decreased T_3	Decreased secretion of other hormones

Treatment. The goal with hypothyroidism is to restore the metabolic state with T4.

Note

Increase T4 dose by 30–50% during pregnancy.

- In the elderly and those with CAD, this should be done gradually: start with 25–50 mcg and slowly increase.
- In young patients without CAD, start with a weight-based dose of T4, ~100 ug/d.
  - Monitor TSH, T3, and T4 (it takes 6 weeks to equilibrate).
  - T4 must be taken on an empty stomach with no other drugs or vitamins (e.g., calcium, iron, PPIs), as they can decrease its absorption.
- If there is a strong suspicion of suprathyroid hypothyroidism with a hypothalamic or pituitary origin, give hydrocortisone with thyroid hormones. If there is known suprathyroid hypothyroidism, use T4 level—not TSH—to guide treatment.
- If patients require very high doses of T4 and still have elevated TSH, they have malabsorption, so look for celiac sprue.
- During pregnancy, demand for thyroid hormones may increase, so monitor closely. Treat hypothyroidism with T4 (may need 30–50% increase), and target TSH in the lower reference range. Measure TSH at 4–6 weeks' gestation, then every 4–6 weeks until 20 weeks' gestation.

Subclinical hypothyroidism

Subclincal hypothyroidism is an early, mild form of hypothyroidism, with increased TSH and normal T4.

Treat when TSH >10 uU/mL, patient has difficulty conceiving, or there are symptoms of hypothyroidism. Repeat TSH in 6–8 weeks to confirm.

Myxedema coma

Myxedema coma can result if severe, chronic hypothyroidism is left untreated. It is precipitated by cold exposure, trauma, infections, and CNS depressants. It is associated with respiratory depression (CO_2 retention), hypotension, bradycardia, hypoglycemia, and hyponatremia.

Patients develop a hypothermic, stuporous state that is frequently fatal.

Treatment is very high doses of T4 and hydrocortisone (until concomitant adrenal insufficiency has been ruled out with a cosyntropin stimulation test).

Lymphocytic thyroiditis

Lymphocytic thyroiditis (silent, painless, or postpartum thyroiditis) is a self-limiting episode of thyrotoxicosis associated with chronic lymphocytic thyroiditis. It is common in women of any age. The etiology and pathogenesis are unclear.

- Thyroid is nontender, firm, symmetric, and slightly enlarged.
- Characteristic sequence of symptoms is hyperthyroidism, followed by hypothyroidism, and then recovery.
- Lab findings include elevated T3/T4, low RAIU, and normal ESR.
- If antithyroid antibodies are present, they are only in low titer.
- May last for 2–5 months and be recurrent (as in postpartum thyroiditis)

Reidel thyroiditis

Reidel thyroiditis results from intense fibrosis of the thyroid and surrounding structures (including mediastinal and retroperitoneal fibrosis).

Treatment is symptomatic with propranolol.

Neoplasia of the Thyroid

- **Papillary carcinoma** (most common thyroid cancer, nearly 70%) is associated with history of radiation exposure. Women > men by 2–3×.
  - Bimodal frequency: peaks occur in decades 2 and 3, and then again later in life
  - Slow-growing; spreads via lymphatics after many years
  - Treatment is surgery (for small tumors limited to single area of thyroid) or surgery plus radiation (for large tumors); TSH suppression therapy with T4 is also used
- **Follicular carcinoma** (15–20% of all thyroid cancers) is common in the elderly. Women > men.
  - More malignant than papillary carcinoma
  - Spreads hematogenously with distant metastasis to the lung and bone
  - Treatment is near total thyroidectomy with postoperative radioiodine ablation
- **Medullary carcinoma** (5% of all thyroid cancers) occurs as a sporadic form or familial form. It arises from parafollicular cells of the thyroid.
  - More malignant than follicular carcinoma
  - In familial form, families have no other associated endocrine dysfunctions
  - Often produces calcitonin (is the only thyroid cancer with elevated calcitonin)
  - Is the component of 2 types of MEN (multiple endocrine neoplasia)
    - In MEN type IIa (Sipple syndrome), pheochromocytoma, medullary thyroid carcinoma, and (in 50% of cases) parathyroid hyperplasia occur.
    - In MEN type IIb, pheochromocytoma, medullary carcinoma, and neuromas occur.

Note

With **nonthyroidal illness syndrome** (previously called *euthyroid sick syndrome*), acutely ill patients have low free T4, low TSH and very low T3. The condition will normalize in 4–8 weeks. No treatment is needed.

Note

Estrogen increases liver production of TBG, while testosterone reduces liver production of TBG.

Note

Calcitonin can be elevated with cancer of the lung, pancreas, breast, and colon. However, of the **thyroid cancers, calcitonin is elevated only with medullary carcinoma**.

- **Thyroid adenoma (benign tumor)** may be nonfunctioning or hyperfunctioning.
  - Categorized as follicular (**most common**; highly differentiated, autonomous nodule), papillary, or Hürthle.
  - Slow-growing
  - Treatment for hyperfunctioning adenoma is ablation containing radioactive iodine.

Clinical Correlate

RET mutations are the mutations associated with MEN2 and familial medullary thyroid carcinomas.

Thyroid carcinoma should be suspected with the following:

- Recent growth of thyroid or mass with no tenderness or hoarseness
- History of radiation to the head, neck, or upper mediastinum in childhood (takes ~30 years to develop thyroid cancer)
- Presence of a solitary nodule or calcitonin production
- Calcifications on x-ray such as psammoma bodies suggest papillary carcinoma.
- Do thyroid function tests first; cancer is never hyperfunctioning.
- Increased density on x-ray suggest medullary carcinoma.

Note

Thyroglobulin is secreted by papillary and follicular carcinoma and is a marker for recurrent/persistent disease. After thyroidectomy, check thyroglobulin at 6 months and then annually.

For a solitary nonfunctioning nodule, diagnostic tests include:

- TSH; if normal, then proceed to FNA
- FNA for cytology in most cases
  - Nonfunctioning thyroid nodules prove to be malignant in a small number of cases.
  - Functioning nodules are very seldom malignant.
- U/S to distinguish cysts from solid nodules

Clinical Recall

Which of the following is the best initial step (most sensitive test) for the diagnosis of suspected hyperthyroidism?

A. RAIU scan

B. Free T4 level

C. Free T3 level

D. TSH level

E. TSI including antithyroglobulin and antimicrosomal Ab

Answer: D

PARATHYROID GLANDS

The function of parathyroid hormone (PTH) is to maintain extracellular fluid calcium concentration.

- Acts directly on the bone and kidney, and indirectly on intestine (through its effects on synthesis of 1,25-dihydroxycholecalciferol [$1,25(OH)_2D_3$]) to increase serum calcium
- Is closely regulated by the concentration of serum-ionized calcium
- Increases osteoclast activity, which releases calcium
- Inhibits phosphate reabsorption in the kidney tubule, also favoring bone dissolution and calcium release from bones
- Activates vitamin D, which increases the GI absorption of calcium

Calcium regulation involves the following:

- **Three tissues**: bone, kidney, intestine
- **Three hormones**: PTH (hypercalcemic), calcitonin (hypocalcemic), and activated vitamin D (hypercalcemic)

Hypocalcemia

Hypocalcemia is insufficient calcium in the blood. Causes include:

- Hypoparathyroidism (the parathyroid glands secrete insufficient amounts of PTH, leading to hyperphosphatemia [causes phosphate to elevate because PTH is essential for renal excretion of phosphate])
  - Surgical removal of the thyroid (**most common cause of hypoparathyroidism**)
  - Hereditary hypoparathyroidism (DiGeorge syndrome)
  - Acquired hypoparathyroidism (surgical removal)
- Hypomagnesemia (magnesium deficiency, seen with decreased GI absorption and alcoholism; prevents release of PTH from the gland)
- Autosomal dominant hypocalcemia (genetic disorder with an activating mutation in the CaS receptors)
  - Usually when CaS receptors are activated by calcium, PTH is suppressed (negative feedback inhibition)
  - When there is an activating mutation of the CaS receptor, it is always activated, so PTH is always suppressed, leading to low calcium and hyperphosphatemia

Hypocalcemia is also seen in:

- Renal failure (*hyper*phosphatemia, elevated PTH, and low 1,25-dihydroxyvitamin D)
- Vitamin D deficiency (*hypo*phosphatemia) (vitamin D is needed for intestinal absorption of calcium and phosphate)
- Drugs such as loop diuretics, phenytoin, alendronate, and foscarnet
- Pseudohypoparathyroidism (resistance to PTH), elevated PTH, and hyperphosphatemia
- Massive blood transfusion, due to binding of the calcium to the citrate in the transfused blood

- Low magnesium, due to malnutrition with alcoholism (preventing the release of PTH from the parathyroid glands)
- Alkalosis, decreasing free calcium by causing increased binding of calcium to albumin
- Pseudo hypocalcemia, which occurs with low albumin; normal free calcium, and decreased total calcium

Clinical Findings. Hypocalcemia results in increased neural hyperexcitability. Symptoms depend on the level of calcium, duration, acid-base disorder, and age at onset.

- Neuromuscular irritability: tetany, laryngospasm, cramping, seizures, impaired memory function
- Possible positive Chvostek sign (percussion of the facial nerve in front of ear, which elicits a contraction of facial muscles and upper lip)
- Possible positive Trousseau sign (inflation of a BP cuff on the arm to a pressure higher than patient's systolic BP for 3 min elicits flexion of the metacarpophalangeal joints and extension of interphalangeal joints)
- Ocular findings: cataracts, soft tissue calcifications
- Possible cardiovascular effects: QT prolongation, refractory CHF, and/or hypotension

Diagnosis is suggested when serum calcium is low; it is important to check albumin and make the correction in calcium level.

- Low calcium may be due to low albumin; for a 1.0 g/dL drop in albumin, total calcium will decrease by 0.8 mg/dL. It is better to measure ionized calcium.
- PTH can be low (hypoparathyroidism) or high.
- **Low calcium + high phosphorous** can be due to renal failure, massive tissue destruction, hypoparathyroidism, or pseudohypoparathyroidism. **Low calcium + low phosphorous** can be due to absent/ineffective vitamin D.

Treatment.

- Acute disease: IV calcium gluconate
- Chronic disease
  - Kidney failure: calcitriol (1,25-dihydroxyvitamin D)
  - Liver failure: 25-hydroxycholecalciferol and calcium
  - Vitamin D deficiency: high dose cholecalciferol (D3) or ergocalciferol (D2) and calcium
  - Hypoparathyroidism: calcitriol and calcium

Correct hypomagnesemia if present. Overtreatment can cause kidney stones.

Hypercalcemia

Hypercalcemia is elevated total or free calcium in the blood.

- About 98% of calcium is stored in bone. Calcium is absorbed from the proximal portion of the small intestine, particularly the duodenum.
- About 80% of an ingested calcium load in the diet is lost in the feces, unabsorbed.
- Of the 2% of calcium that is circulating in blood, free calcium is 50%, protein bound is 40%, with only 10% bound to citrate or phosphate buffers.

Causes of hypercalcemia include:

- Primary hyperparathyroidism (**most common**), usually asymptomatic and found on routine testing
- Malignancy such as SCC, renal cell, bladder, breast cancer, which produce a PTH-related protein
- Granulomatous disease such as sarcoidosis, TB, berylliosis, histoplasmosis, and coccidioidomycosis or lymphoma
- Vitamin D intoxication, thiazide diuretics, lithium, and Paget disease, as well as prolonged immobilization (all rare)
- Hyperthyroidism, due to a partial effect of thyroid hormone on osteoclasts
- Acidosis, due to increased free calcium (because albumin buffers acidosis, and increased binding of hydrogen ions to albumin results in the displacement of calcium from albumin)
- Multiple myeloma, due to lytic bone disease (cytokines activate osteoclasts)

Note

In granulomas, macrophages have their own 25-vitamin D hydroxylation, producing active 1,25 vitamin D (**high-yield fact**).

Familial hypocalciuric hypercalcemia (FHH)

- Benign form of hypercalcemia
- Presents with mild hypercalcemia, urine calcium to creatinine ratio <0.01, and urine calcium <200 mg/day (hypocalciuria)
- Most patients have a family history of hypercalcemia
- Associated with a loss of function mutations in the CaSR gene, which encodes a calcium-sensing receptor (expressed in kidney and parathyroid tissue); the perceived lack of calcium level by the parathyroid leads to high levels of parathyroid hormone
- Indicated by the presence of both hypercalcemia and hypocalciuria
- No treatment is needed, since patients typically asymptomatic

Note

- FHH will result in both hypercalcemia and hypocalciuria.
- In all other causes of hypercalcemia, elevated blood calcium is correlated with elevated urine calcium (as a properly sensing kidney works to excrete calcium).

Clinical Presentation.

- Neurologic: decreased mental activity such as lethargy and confusion
- GI: decreased bowel activity such as constipation and anorexia but also possible nausea and vomiting; pancreatitis due to precipitation of calcium in the pancreas
- Possible ulcer disease (unclear reasons)
- Renal: polyuria and polydipsia due induction of NDI; calcium precipitation in the kidney, causing kidney stones and nephrolithiasis
- Cardiovascular: hypertension (30–50% of patients); ECG will show a short QT

Note

While pancreatitis is associated with *hyper*calcemia, **severe pancreatitis** is associated with *hypo*calcemia because calcium binds to malabsorbed fat in the intestine.

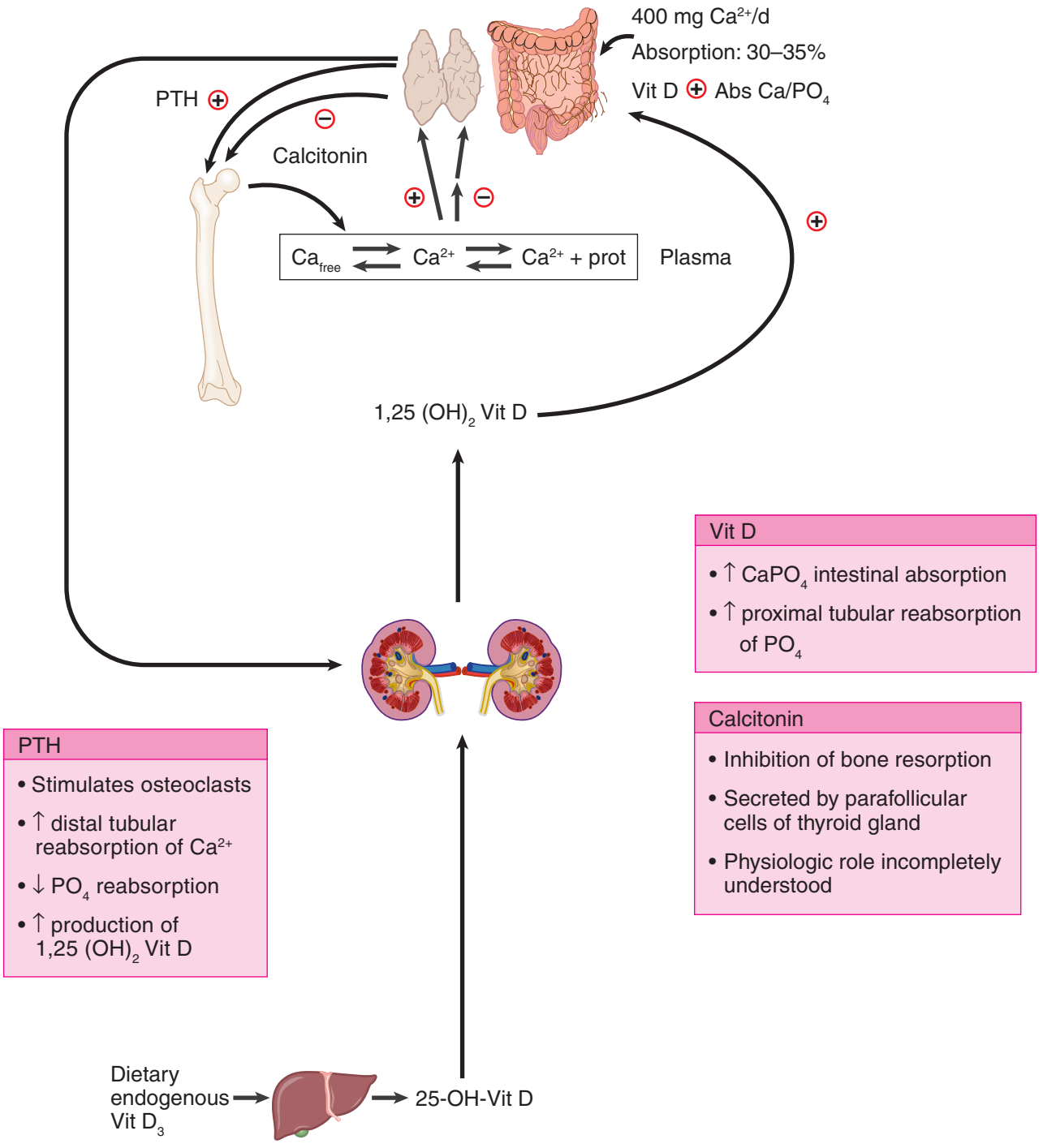
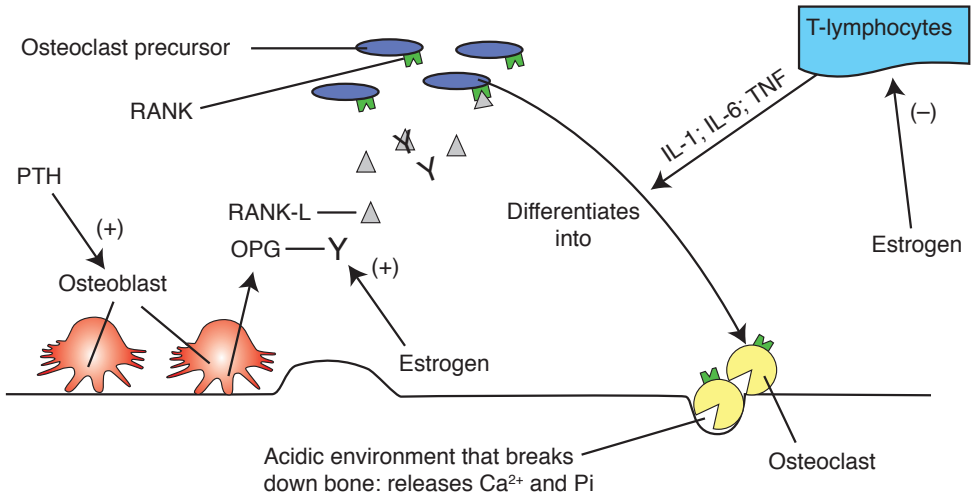


Figure 2-10. Calcium Regulation

Treatment. For severe, life-threatening hypercalcemia, give the following:

- Vigorous fluid replacement with normal or half-normal saline
- IV bisphosphonate such as zoledronate or pamidronate to inhibit osteoclasts and stimulate osteoblasts (maximum effect takes 2–3 days)
- If fluid replacement and diuretics do not lower the calcium level quickly enough and you cannot wait the 2 days for the bisphosphonates to work, use calcitonin
  - Calcitonin inhibits osteoclasts.
  - After 48 hours, calcitonin can cause tachyphylaxis.
- Prednisone for elevated 1,25-di-hydroxyvitamin D (granulomas or lymphoma), or multiple myeloma
- Hemodialysis for severe hypercalcemia and oliguric renal failure

Loop diuretics are not recommended for hypercalcemia unless the patient has heart failure, renal failure, or volume-overload after aggressive IVFs.



RANK = receptor activator of nuclear factor kappaB

RANK-L = receptor activator of nuclear factor kappaB ligand

OPG = osteoprotegerin (endogenous blocker of RANK-L)

Pi = phosphate

Figure 2-11. Relationship between Osteoblasts and Osteoclasts

Note

With hypercalcemia:

- Calcitonin is an intermediary measure while waiting for IV bisphosphonate to act.
- Bisphosphonates cannot be used with renal failure.

Hyperparathyroidism

There are 3 types of hyperparathyroidism.

- **Primary** hyperparathyroidism (**most common condition of mild hypercalcemia**) is caused by a hyperfunction of the parathyroid glands.
  - Most commonly, the oversecretion of PTH is caused by a parathyroid adenoma of one gland (hyperplasia of all 4 glands is a less common cause, and parathyroid cancer is a rare cause).
  - Elevated PTH then causes elevated serum calcium and low serum phosphate.
  - Can be seen with MEN
    - In MEN type I, hyperparathyroidism, pituitary tumors (3 "Ps"), and pancreatic tumors are seen.
    - In MEN type II, hyperparathyroidism, pheochromocytoma, and medullary carcinoma of the thyroid are seen.
- **Secondary** hyperparathyroidism is due to physiologic (i.e., appropriate) secretion of PTH by the parathyroid glands in response to hypocalcemia resulting from vitamin D deficiency or chronic kidney disease.
  - Serum calcium is low (causing the elevated PTH).
  - In the case of chronic kidney failure and anuria, phosphate is elevated (the kidney is unable to 'trash' phosphate).
  - Phosphate is low.
  - Prolonged vitamin D deficiency can also lead to elevated PTH (seen in intestinal malabsorption and vitamin D-dependent rickets, type II). Symptoms include osteomalacia, bone pain/muscle weakness, and fractures. Calcitriol (activated vitamin D) increases intestinal absorption of calcium and phosphate. To diagnose, test 25-hydroxy-vitamin D; level <30 mg/mL is consistent with deficiency.
- **Tertiary** hyperparathyroidism is seen with long-term secondary hyperparathyroidism, which can lead to hyperplasia of the parathyroid glands and a loss of response to serum calcium levels.
  - Most commonly seen in patients with chronic renal failure.
  - Is an autonomous activity of the parathyroid glands.
  - Hypercalcemia and hyperphosphatemia will be seen.
  - Treatment is surgical removal.

Clinical Findings. About 50% of patients with hyperparathyroidism are asymptomatic. When symptoms do occur, they include:

- Osteitis fibrosa cystica due to increased rate of osteoclastic bone resorption; will cause bone pain, fractures, swelling, deformity, areas of demineralization, bone cysts, and brown tumors (punched-out lesions producing a salt-and-pepper-like appearance)
- Urinary tract manifestations, including polyuria, polydipsia, stones, and nephrocalcinosis with renal failure (the polyuria and polydipsia are from NDI)
- Neurologic manifestations, including CNS problems, mild personality disturbance, severe psychiatric disorders, mental obtundation or coma, neuromuscular weakness, easy fatigability, and atrophy of muscles

Note

- Think of vitamin D deficiency in cases of low phosphate and low calcium.
- To diagnose, test 25-hydroxy-vitamin D (not 1,25-di-hydroxy-vitamin D) for the following reasons:
  - Most total body stores of vitamin D are in the form of 25-hydroxy-vitamin D (with a very small amount activated).
  - 25-hydroxy-vitamin D has a longer half-life than 1,25-di.

Clinical Correlate

Prolonged vitamin D deficiency can also lead to elevated PTH (seen in intestinal malabsorption and vitamin D-dependent rickets, type II). Symptoms include osteomalacia, bone pain/muscle weakness, and fractures. Calcitriol (activated vitamin D) increases intestinal absorption of calcium and phosphate. To diagnose, test 25-hydroxy-vitamin D (not 1,25-di-hydroxy-vitamin D) because most total body stores of vitamin D are in the form of 25-hydroxy-vitamin D, with a very small amount activated. Also, 25-hydroxy-vitamin D has a longer half-life. Level <30 mg/mL is consistent with deficiency.

- GI manifestations, including anorexia/weight loss, constipation, nausea/vomiting, thirst, abdominal pain with pancreatitis, and peptic ulcer disease
- Cardiovascular findings, including hypertension and arrhythmias (short QT)

Diagnosis.

- Serum calcium >10.5 mg/dL
- Elevated PTH
- Elevated urine calcium (80%) (but some patients have normal level due to the calcium-reabsorbing action of PTH)
- Low serum phosphate (<2.5 mg/dL)

Imaging studies such as CT, MRI, sonography, and nuclear scan are not used to diagnose hyperparathyroidism. A nuclear parathyroid scan (sestamibi) can be used to localize the adenoma. When combined with a neck sonogram, specificity rises significantly.

Note

In every other cause of hypercalcemia, the PTH level will be low. In primary hyperparathyroidism, PTH is always elevated.

Treatment.

Primary hyperparathyroidism.

- Surgery (those age <50)
  - Indications include symptoms of hypercalcemia; serum calcium >1 mg/dL above normal; GFR <60 mL/min; T-score <-2.5; kidney stones; and 24-hour urine calcium >400 mg/day.
  - Before surgery, do sestamibi scan to look for an adenoma; also check 25-hydroxyvitamin D level; if a deficiency exists, correct before surgery, as vitamin D deficiency increases the risk of hungry bone syndrome.
  - Hungry bone syndrome is severe hypocalcemia after parathyroidectomy due to relative hypoparathyroidism and reduced PTH-mediated production of activated vitamin D culminating in rapid influx of calcium into bone.
- If surgery is not needed
  - Calcium, creatinine, and GFR measurement every year
  - BMD measurement every 2 years
- If surgery is contraindicated
  - Medical treatment with bisphosphonates (pamidronate)
  - Reduced dietary calcium to 400 mg/d
  - Oral hydration with 2–3 L of fluid; phosphate supplementation with phospho-soda

Note

Calcitonin is an intermediary measure while waiting for IV bisphosphonate to act.

Secondary hyperparathyroidism.

- Check for and correct vitamin D
- Correct hyperphosphatemia first with a phosphate-binder such as calcium acetate or sevelamer and lanthanum
- If still no response to PTH level, give calcitriol
  - Activated vitamin D suppresses PTH release by negative feedback inhibition on the parathyroid glands.
  - Phosphate must be <5.5 mg/dL before giving calcitriol because it can increase intestinal absorption of phosphate.

Note

Half of all patients with primary hyperparathyroidism also have vitamin D deficiency, and serum calcium will be even higher after that deficiency is corrected. Check vitamin D in all patients with primary hyperparathyroidism.

- Cinacalcet, a calcimimetic agent which shuts off the parathyroids, will increase the sensitivity of calcium-sensing receptors to calcium (basolateral membrane potential) on the parathyroid and suppress PTH secretion (side effects include hypocalcemia); it is used only for select circumstances:
  - Patients on hemodialysis
  - Hypercalcemia in patients with parathyroid carcinoma
  - Patients with moderate-to-severe primary hyperparathyroidism unamenable to surgery

Tertiary hyperparathyroidism.

- Parathyroidectomy is usually necessary.

Note

Hyperparathyroidism can cause pseudogout (look for chondrocalcinosis).

Hypoparathyroidism

See section on ***Hypocalcemia***.

Clinical Recall

Which of the following is a clear indication for surgery in a patient with primary hyperparathyroidism?

A. Calcium level 10.5 mg/dL

B. Creatinine level 1.0 mg/dL

C. ECG showing prolonged QT interval

D. Male gender, age 38

E. DEXA T-score +1.0

Answer: D

Osteoporosis

Osteoporosis is a disease of decreased bone mass leading to increase fractures. Causes include:

- Estrogen deficiency in women (**most common**)
- Secondary causes (**high yield**)
  - Testosterone deficiency (any man with osteoporosis should have testosterone level checked)
  - Hyperthyroidism
  - Hyperparathyroidism
  - Cushing syndrome
  - Cirrhosis
  - Malabsorption (celiac, Crohn disease)
  - Rheumatoid arthritis
  - CKD

  - Vitamin D deficiency
  - Medications (steroids, excessive thyroid hormone, phenytoin, phenobarbital, thiazolidinediones, PPI)
  - Multiple myeloma

Diagnosis is made with the following:

- BMD test with DEXA scan for women age ≥65 and premenopausal women at increased risk (i.e., RA, glucocorticoid use, hyperparathyroidism, malabsorption/celiac sprue).
  - **Osteopenia**: DEXA T-score –1.0 to –2.4
  - **Osteoporosis**: DEXA T-score <–2.5
- History of fragility fracture (fall from standing height or lower)

All patients diagnosed with osteoporosis should have the following checked:

- CBC, TSH, LFTs
- Calcium, phosphorous
- Creatinine
- 25-hydroxy-vitamin D
- tTG antibodies (if celiac is suspected)
- Cushing work-up if there are features of Cushing syndrome

Treatment. Start with smoking cessation, alcohol reduction, resistance exercises, and supplemental calcium/vitamin D. Medical therapy includes:

- Bisphosphonates: alendronate or risedronate (**first-line**)
  - Oral bisphosphonates can lead to pill esophagitis.
  - IV bisphosphonates and denosumab can cause osteonecrosis of the jaw.
- Denosumab (monoclonal antibody that inhibits RANK-L and decreases osteoclast activity) in stage 4 CKD and intolerant/incomplete response to bisphosphonates
- Teriparatide (synthetic PTH) increases bone formation and bone mass
- Calcitonin for pain from fractures
- Teriparatide is associated with osteosarcoma; use for 2 years at most

For osteoporosis, do not use the following:

- Estrogen replacement
- Combination teriparatide + a bisphosphonate
- Combination bisphosphate + CKD (use denosumab instead) and hypocalcemia

Osteomalacia

Osteomalacia is a metabolic bone disease resulting from failure of organic matrix of bone to mineralize because of lack of calcium or phosphorus.

Symptoms and signs include:

- Bone pain, fatigability
- Proximal muscle weakness
- Hypocalcemia and hypophosphatemia
- Elevated alkaline phosphatase

Diagnosis is made with vitamin D testing.

Treatment is high-dose ergocalciferol or cholecalciferol.

Paget Disease of the Bone

Paget is increased bone remodeling, leading to accelerated rates of bone turnover and disruption of the normal architecture of bone and deformities of bone (enlargement of the skull, bowing of the femur). Most patients are asymptomatic and will have incidental x-ray findings or elevated alkaline phosphatase on routine labs.

Symptoms and signs include bone pain; fractures; high-output cardiac failure (**most common cause of death**); cranial nerve compression; and spinal stenosis.

Diagnosis is made with the following:

- Elevated alkaline phosphatase
- X-ray showing focal osteolysis with coarsening of the trabecular pattern (sclerotic bone), cotton wool skull and cortical thickening (bone scan must be ordered to evaluate extent of disease)
- Calcium and PTH are usually normal

Treatment is bisphosphonates if there is bone pain, radiculopathy, or involvement of a weight-bearing bone.

DISORDERS OF THE EXOCRINE PANCREAS

Diabetes Mellitus

Diabetes mellitus (DM) is a disorder of carbohydrate metabolism, affecting 20% of patients age >65 in the United States. Causes include:

- Relative or absolute deficiency of insulin
- Hyperglycemia
- End-organ complications (e.g., nephropathy, retinopathy, neuropathy, accelerated atherosclerosis)

There are 2 types of DM, but **type 2 is far more common**.

- **Type 1 IDDM (insulin-dependent or juvenile onset)** (5–10% of diabetes worldwide, most likely autoimmune)
  - Males = females
  - Age of onset usually age <30
  - Genetically, <10% of first-degree relatives are affected with a 50% occurrence in identical twins
  - Increased prevalence of autoantibodies to islet cells, glutamic acid decarboxylase (GAD), and other tissues with IDDM
  - Associated with HLA-B8, HLA-B15, HLA-DR3, and HLA-DR4
  - Body build usually lean
  - Patients prone to ketosis owing to absent insulin production
  - By the time the condition appears, most of the beta cells in the pancreas destroyed
  - High prevalence of other autoimmune disorders, such as celiac disease, Graves, hypothyroidism, Addison, pernicious anemia, vertigo
    - Think of this diagnosis if age 35–50, BMI <25, acute onset, personal or family history of autoimmune disease
    - Anti-glutamic acid decarboxylase, anti-islet cell, antibodies to tyrosine phosphatase IA-2 will be positive.
    - C-peptide is not helpful in determining type I vs type II because it can be low in DM II also
- **Type 2, or NIDDM (non-insulin-dependent or maturity onset)** (90% of cases)
  - Males > females
  - Age of onset usually age 40
  - Genetically >20% of first-degree relatives are affected with 90–100% occurrence in identical twins
  - No associated autoantibodies
  - Body build usually obese (most are >15% above ideal body weight)
  - Patients are ketosis-resistant, and insulin levels may be high, normal, or low
  - Two clear physiologic defects: abnormal insulin secretion and resistance to insulin action in target tissues
  - Progresses because beta-cells burn out, not because insulin resistance gets worse

Clinical Findings. Symptoms vary by patient, but commonly hyperglycemia, polyuria, polydipsia, polyphagia, ketonuria, and weight loss are seen.

- First event may be an acute metabolic decompensation, resulting in coma (ketoacidosis for IDDM and hyperosmolar coma for NIDDM)
- Occasionally, initial symptom of DM is a degenerative complication like neuropathy

Note

Type 2 diabetes progresses because of loss of beta-cells, not because of worsening inulin-resistance.

Diagnosis.

- In **asymptomatic** patients: elevated plasma or urine glucose during routine screening does not establish diagnosis but indicates a need for further evaluation.
- In **symptomatic** patients: polyuria, polydipsia, ketonuria, and weight loss.
  - Plasma glucose >200 mg/dL is sufficient for diagnosis with no further testing needed; random glucose >200 mg/dL is diagnostic
  - Fasting plasma glucose ≥126 mg/dL on 2 occasions; DM is diagnosed when plasma glucose ≥200 mg/dL at 2 h and on at least one of the earlier samples
  - HbA1c >6.5% is diagnostic of diabetes

If 2 separate tests are done and one is normal, repeat the abnormal test:

- A1C is falsely low in hemolytic anemia, chronic kidney disease. Use finger sticks for more accurate measurements.
- A1C is falsely high in iron deficiency due to increase proportion of older erythrocytes.

Glycosylated hemoglobin A_{1c} (HbA_{1c}) is produced by nonenzymatic condensation of glucose molecules with free amino groups on the globin component of hemoglobin. It is used both for diagnosis and to follow compliance of the treatment and glucose control in diabetic patients. HbA_{1c} is high in diabetics with chronic hyperglycemia during the preceding 8–12 weeks.

- In young patients, goal A1C is 7%.
- In older patients and young patients with long-term complications (ie, renal failure, blind), goal is 8%.

Treatment. The objectives of diabetic therapy are to control symptoms, prevent acute complications, and limit long-term complications. The goal is HbA1c <7%. Patient education is essential.

- Weight loss, low-fat diet, exercise (up to 25% success rate with this alone): reduction of as little as 4–7% body fat has an enormous effect on peripheral insulin sensitivity and on reduction of postprandial hyperglycemia
- When diet and exercise do not keep HbA1c <7%, medications are introduced.
  - Oral hypoglycemic should be used for all patients with type 2 DM
  - Metformin (**first-line**) and lifestyle intervention should be used for all newly diagnosed patients
    - Metformin is safe and should be used in moderate renal failure (do not use if GFR <30 mL/min and use lower dose if 30–45 mL/min)
    - Does not cause hypoglycemia or weight gain
    - Start at a low dose and slowly increase to avoid GI side effects
    - Side effects include vitamin B12 deficiency and lactic acidosis (very rare)

Note

Oral glucose tolerance test is rarely required in DM.

Clinical Correlate

Exercise lowers glucose level:

- Exercising muscle needs no insulin for glucose to enter.
- Resting muscle needs insulin for glucose entry.

The effects of diet, exercise, and weight loss can last for years.

In all cases, **metformin is the best initial treatment for type 2 DM**. After metformin, add-on drugs include:

- Incretin mimetics (exenatide, liraglutide), direct analogues of GLP-1 except their actions last much longer; given by subcutaneous injection
  - **First-line** for obese patients to promote weight loss; augment the naturally occurring hormones secreted from GI tract in response to food (when food enters the intestine, incretins are released)
  - Proven to reduce A1C up to 2%
  - Slow gastric motility (nausea and vomiting are main side effects); may increase risk of pancreatitis so do not use if history of pancreatitis
  - Increase the release of insulin from the pancreas in a glucose-dependent matter, i.e., only if there is hyperglycemia (very rarely cause hypoglycemia)
  - Inhibit glucagon release
  - Liraglutide significantly reduces cardiovascular death and all-cause mortality; use on anyone with diabetes and cardiovascular disease
- Dipeptidyl peptidase IV (DPP-IV) inhibitors (sitagliptin, saxagliptin, linagliptin, alogliptin): inhibit the metabolism of the incretins GIP and GLP-1; given orally
  - Increase insulin release from the pancreas and slow stomach emptying
  - Weight-neutral
  - Less effective than GLP-1 analogs (GLP-1 analogs are preferred in young, obese patients and those with CAD)
  - Safe in renal failure
- Sodium-glucose co-transporter 2 (SGLT2) inhibitors (canagliflozin, dapagliflozin, empagliflozin, all equal in efficacy) inhibit reabsorption of glucose in the proximal tubules, leading to increased renal excretion of glucose; given orally
  - Cause weight loss 2–3 kg
  - Lower BP and can lead to orthostatic hypotension
  - Use for DM with urine albumin >300 or if GFR >30 ml/minute
  - Side effects include increased risk of genital candida infections, UTI, euglycemic DKA
- Empagliflozin significantly reduces rates of death by CVD, all-cause mortality, and hospitalization for HF (and is FDA-approved for reduction of CV death in adults with type 2 DM and CVD). Also reduces progression of nephropathy (defined as progression to macroalbuminuria, doubling of serum creatinine, initiation of renal replacement therapy, or death from renal disease).
- Canagliflozin is associated with increased risk of amputation (do not use if history of PVD, previous amputations, diabetic ulcer or neuropathy)
- Thiazolidinediones (rosiglitazone, pioglitazone) can worsen CHF. They are thought to act by decreasing the resistance of tissues to insulin. Side effects include weight gain and osteoporosis. Pioglitazone may be linked to bladder cancer.
- Sulfonylureas (glyburide, glipizide, glimepiride) cause insulin secretion from beta-cells. Side effects include weight gain and hypoglycemia. They are used less commonly because of their side effects and lack of proven CVD benefit that is seen in the other agents.

- **Insulin** regimen can be started anytime (will cause weight gain)
  - Start with basal insulin only. If A1C is high but fasting is at goal (80–130), check postprandial 2 hours after a meal. Goal postprandial is <180. Add bolus insulin or meglitinides to control postprandial.
  - Add metformin, GLP-1 analogs, and SGLT2 inhibitors to insulin (leads to better glycemic control and weight loss)
  - When starting insulin, divide 50% into long-acting and 50% into pre-meal short-acting.
    - Usually given as glargine insulin 1×/day injection + 2–3×/day ultra short-acting insulin such as lispro or aspart before meals
    - Glargine causes fewer episodes of hypoglycemia than NPH
    - Levemir is newer, long-acting insulin, lasting 16–18 hours

Note

If weight loss is desired, use GLP-1 analogs, pramlintide, or SGLT2 inhibitors.

Table 2-3. Oral Hypoglycemic Drugs

Class	Generic Name
Sulfonylureas	Glyburide, glipizide, glimepiride
Biguanides	Metformin
Thiazolidinediones	Rosiglitazone, pioglitazone
Glucosidase inhibitors	Acarbose, miglitol
Meglitinides	Repaglinide, nateglinide
DPP-IV inhibitors	Sitagliptin, saxagliptin, linagliptin
Subcutaneous agents	
GLP-1	Exenatide, liraglutide
SGLT2 inhibitors	Canagliflozin, dapagliflozin, empagliflozin
Amylin mimetic	Pramlintide (suppresses plasma glucagon secretion; slows gastric emptying and promotes satiety; decreases postprandial glucose rise; and causes weight loss)

Table 2-4. Insulin Preparations

Type	Peak Action (Hours)	Duration of Action (Hours)
Ultra-short-acting		
Insulin lispro Insulin aspart	30–60 min 20–30 min	4–6 3–5
Rapid (given 5–15 min before meals)		
Regular Semilente Glulisine (given 30 min before meals)	2–4 2–6	6–8 10–12
Intermediate		
NPH Lente	6–12 6–12	12–18 12–18
Long-acting		
Glargine Levemir Degludec	2 18–24	24 36

Clinical Recall

Which of the following is the best initial drug to start in a patient with newly diagnosed non-insulin-dependent DM?

A. PO glyburide

B. PO chlorpropamide

C. PO acarbose

D. IM insulin glargine

E. PO metformin

Answer: E

Bariatric procedures should be considered in obese patients.

There are several important complications that can result from untreated DM.

- **Acute complications**
  - **Diabetic ketoacidosis (DKA)** (seen in type 1 DM) is a result of severe insulin insufficiency and may be the presenting manifestation. Precipitating factors include insufficient or interrupted insulin therapy, infection, emotional stress, and excessive alcohol ingestion.
    - Symptoms include anorexia, nausea/vomiting, abdominal pain, rapid breathing (Kussmaul respiration), "fruity" breath odor of acetone, signs of dehydration, and altered consciousness to coma. Acidosis can result in fatal rhythm disturbance.
    - Diagnosis is made with elevated blood glucose, increased serum acetoacetate, acetone, hydroxybutyrate, metabolic acidosis (low serum bicarbonate and low blood pH), and increased anion gap (sodium – [bicarbonate + chloride])
    - Treatment is insulin, fluids, and electrolyte replacement, with normal saline in high volumes. Bolus with 5–10 units of regular insulin.
    - Acutely, DKA is associated with hyperkalemia. The total body level of potassium is depleted because of the urinary loss of potassium. As soon as potassium level falls to ≤5 mEq/L, give potassium replacement. Start with IV insulin, then switch to subcutaneous insulin (overlap them both for 6–8 hours) when anion gap normalizes and serum bicarbonate is normal. Add 5% dextrose to the normal saline as blood glucose reaches 200–250 mg/dL and continue IV insulin until the anion gap normalizes. Check potassium before starting IV insulin; if normal (3.3–5.5 mEq/L, start potassium with inulin, but if <3.3 mEq/L, hold insulin and give potassium first).
    - The "honeymoon" period is an initial episode of ketoacidosis followed by a symptom-free interval during which no treatment is required. Presumably, stress-induced epinephrine release blocks insulin secretion, causing the syndrome. In normal individuals insulin reserve is such that hormone release is adequate even in the face of stress.
      - The **Somogyi effect** is rebound hyperglycemia in the morning because of counterregulatory hormone release after an episode of hypoglycemia during the night.
      - The **dawn phenomenon** is an early morning rise in plasma glucose secondary to a rise in counter-regulatory hormones cortisol, epinephrine, and GH requiring increased amounts of insulin to maintain euglycemia.
      - If someone has morning hyperglycemia, check glucose at 2 AM to determine if the cause is Somogyi effect or dawn phenomenon.
  - **Hyperosmolar nonketotic coma (HONK)** (seen in type 2 DM) is characterized by severe hyperglycemia in the absence of significant ketosis. Pathophysiology involved is profound dehydration resulting from a sustained hyperglycemic diuresis. Clinical findings are weakness, polyuria, polydipsia, lethargy, confusion, convulsions, and coma.
    - Precipitating factors include noncompliance of treatment; inability to drink sufficient water to keep up with urinary losses (common in elderly diabetics living in nursing homes); infections; stroke; steroids; immunosuppressant agents; and diuretics.

- Can result after a therapeutic procedure such as peritoneal/hemodialysis, tube feeding of high-protein formulas, or high-carbohydrate infusion.
- Diagnosis is made with elevated blood glucose (typically ≥700 mg/dL) and extremely high serum osmolality (serum osmolality in mOsm/L = 2[sodium] + [glucose/18] + [BUN/2.8]). High BUN (prerenal azotemia) and mild metabolic acidosis (bicarbonate ~20 mEq/L) is also seen without ketosis.
- Treatment is high-volume fluids, electrolyte replacement, and insulin.

- **Chronic complications**
  - **Microvascular** disease of diabetes includes diabetic nephropathy, neuropathy, and retinopathy (glycemic control shows far greater effect on morbidity and mortality).
    - Diabetic nephropathy
      - Hyperproliferation, proteinuria, and end-stage renal disease can develop.
      - The pathology is commonly diffuse and leads to widening of glomerular basement membrane and mesangial thickening. Nodular pathology can occur and results in hyalinization of afferent glomerular arterioles (Kimmelstiel-Wilson syndrome).
      - Treatment is strict control of diabetes, ACE inhibitors, and dialysis or renal transplantation.
    - Diabetic neuropathy
      - **Peripheral** neuropathy (**most common**) is symmetrical, with symptoms of numbness, paresthesia, and pain. Physical exam reveals absent reflexes and loss of vibratory sense.
      - **Mononeuropathy**—vascular in origin—affects a single nerve or nerve trunk (mononeuritis multiplex); symptoms include sudden foot drop, wrist drop, or paralysis of CN III, IV, or VI.
      - **Autonomic neuropathy** can be devastating; most common symptoms include orthostatic hypotension and syncope. Other symptoms include difficulty swallowing, delayed gastric emptying (gastroparesis), constipation, or diarrhea. Diagnosis of gastroparesis is the gastric emptying scintigraphy study. Bladder dysfunction or paralysis can lead to urinary retention. Impotence and retrograde ejaculation can occur (erectile dysfunction is as high as 50% in patients with 10 years of diabetes).
      - Prevention of neuropathy in diabetes is with tight glycemic control. Treatment once it occurs depends on the type. For **peripheral** neuropathy, use gabapentin, pregabalin, amitriptyline (avoid in CAD, as it increases CVD mortality), venlafaxine, duloxetine, capsaicin cream. For **autonomic** neuropathy, use sildenafil for erectile dysfunction and metoclopramide or erythromycin for gastroparesis.
    - Diabetic retinopathy (**most common cause of blindness in middle-aged patients**)
      - Retina is affected; simple or proliferative (microaneurysms, hemorrhages, exudates, retinal edema), where damage can occur
      - Proliferative retinopathy (PDR) is the presence of vitreous hemorrhages or neovascularization (treatment is laser photocoagulation), while nonproliferative (NPDR), or background retinopathy, can only be prevented with tight glucose control

- Pan retinal laser photocoagulation for PDR and severe NPDR
- Intraocular infection of bevacizumab (VEGF inhibitor) or ranibizumab for PDR or severe NPDR

– **Macrovascular** disease of diabetes (very common) includes CAD, peripheral arterial disease, and stroke (glycemic control shows far less effect on morbidity and mortality).
  - Central pathological mechanism is atherosclerosis, which leads to narrowing of arterial walls throughout the body; atherosclerosis is thought to result from chronic inflammation and injury to the arterial wall in the peripheral or coronary vascular system
  - Lipid management includes lipid testing in those with diabetes at least annually goal BP <130/80 mm Hg, and a statin for all those with DM age >40 (regardless of LDL)
  - Risk for death using ASCVD risk score. For **high risk** (10-year ASCVD score ≥7.5%), give high intensity statin, i.e., high-dose atorvastatin or rosuvastatin (except for CKD or age >75 due to risk of rhabdomyolysis). For **moderate risk** (10-year ASCVD risk score <7.5%), give moderate intensity statin, i.e., every other statin or low-dose atorvastatin/rosuvastatin.
  - Do coronary artery bypass in a diabetic patient even if there is only 2-vessel coronary disease.

Diabetes

Most common cause of end-stage renal disease in United States

- Screen all diabetics annually for proteinuria (detectable on standard dipstick when >300 mg/24 hrs.
- Microalbuminuria is defined as 30–300 mg.
- All those with proteinuria should receive treatment with an ACE inhibitor or ARB.

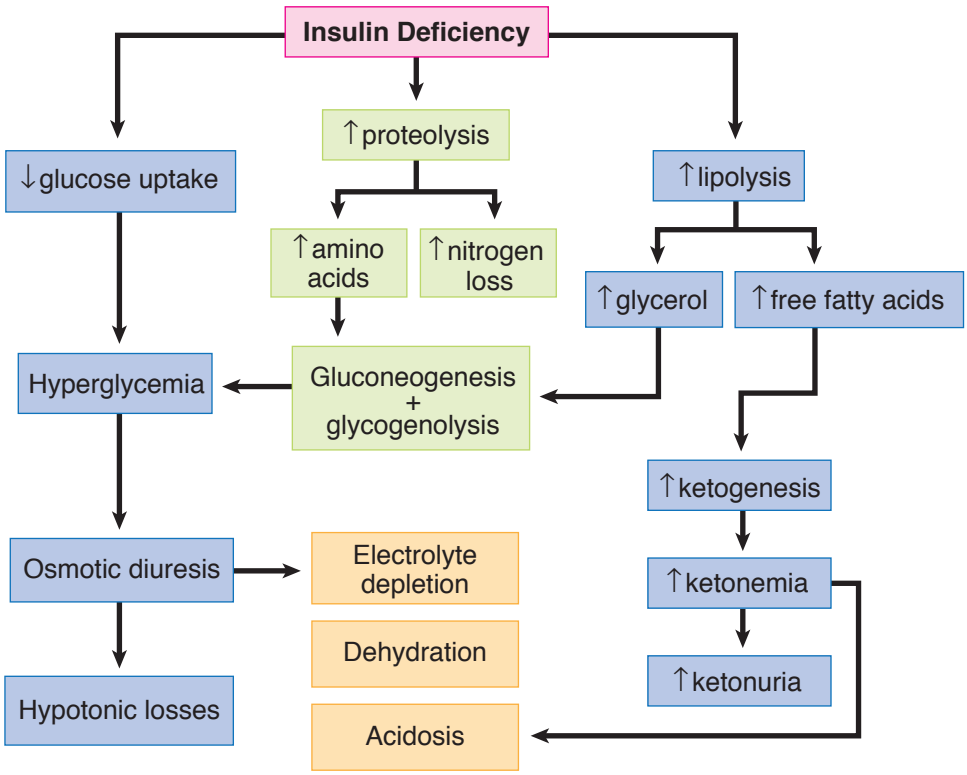
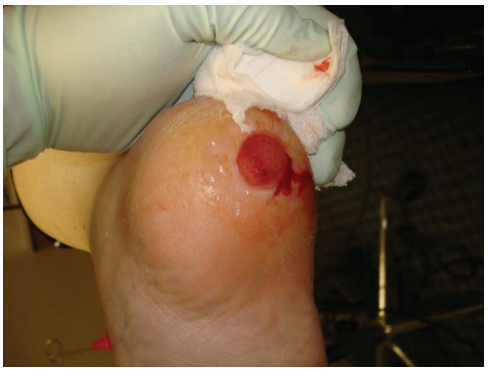


Figure 2-12. Pathophysiology of DKA



Wikimedia, Jonathan Moore

Figure 2-13. Diabetic Foot Ulcer

Note

On the exam, you will be provided with the ASCVD risk score and will not have to calculate.

Note

Macrovascular complications are the most common cause of death in patients with DM. About 75% of deaths result from myocardial infarction, congestive failure, or stroke.

Note

The most common pattern of dyslipidemia in patients with type 2 diabetes is elevated triglyceride and decreased HDL cholesterol.

Hypoglycemia

Glucose is the primary energy source of the brain. Symptoms of low glucose can result from excessive secretion of epinephrine, leading to sweating, tremor, tachycardia, anxiety, and hunger. Hypoglycemia can also result from dysfunction of the CNS, leading to dizziness, headache, clouding vision, blunted mental activity, loss of fine motor skills, convulsions, and loss of consciousness.

There is no uniform correlation between a given level of blood sugar and symptoms. Major symptoms in normal persons may not be seen until blood sugar 20 mg/dL.

- **Postprandial** hypoglycemia (reactive) can be secondary to alimentary hyperinsulinism (after gastrectomy, gastrojejunostomy, pyloroplasty, or vagotomy), idiopathic, and galactosemia.
- **Fasting** hypoglycemia, caused by:
  - Conditions related to the underproduction of glucose, such as hormone deficiencies (panhypopituitarism, adrenal insufficiency), enzyme defects, substrate deficiency (severe malnutrition, late pregnancy), acquired liver disease, or drugs (propanolol, salicylates)
  - Conditions related to overutilization of glucose: hyperinsulinism (which can occur secondary to insulinoma, exogenous insulin, sulfonylureas, drugs [quinine], endotoxic shock, and immune disease with insulin receptor antibodies) and conditions where insulin levels are appropriate, such as extrapancreatic tumors and rare enzyme deficiencies
- **Hypoglycemia caused by insulinoma** (pancreatic B-cell tumor): 90% of these tumors are single and benign. Symptoms include findings of subacute or chronic hypoglycemia, e.g., blurred vision, headache, slurred speech, and weakness. Symptoms occur in the early morning or late afternoon or after fasting or exercise.
  - Factitious hyperinsulinism (common) is caused by self-administration of insulin or ingestion. Most often, patients work in a health profession or have access to drugs through a diabetic family member. A triad of hypoglycemia, high immunoreactivity, insulin, and suppressed plasma C-peptide is pathognomonic of exogenous insulin administration.
  - Ethanol-induced hypoglycemia can occur with prolonged starvation, when glycogen reserves become depleted in 18–24 hours and hepatic glucose output depends completely on gluconeogenesis. Ethanol at a concentration of 45 mg/dL can induce hypoglycemia by blocking gluconeogenesis.

Note

A sulfonylurea screen must be checked before insulinoma can be diagnosed.

Diagnosis is made with serum insulin ≥8 mg/mL in the presence of blood glucose <40 mg/dL (i.e., inappropriately high serum insulin level when glucose is low), noted spontaneously or during a prolonged fast (72 hours). CT scan, U/S, and arteriography may be useful for detecting the tumor(s).

Treatment is surgery, diet, and medical therapy.

Table 2-5. Differential Diagnosis of Insulinoma and Factitious Hyperinsulinism

Test	Insulinoma	Exogenous Insulin	Sulfonylureas
Plasma insulin	High (usually <200 µU/mL)	Very high (usually >1,000 µU/mL)	High
Proinsulin	Increased	Normal or low	Normal
C peptide (insulin connective peptide) 1:1	Increased	Normal or low	Increased
Insulin antibodies	Absent	+/– Present	Absent
Plasma or urine sulfonylurea	Absent	Absent	Present

Clinical Recall

Which of the following medications is contraindicated in patients with acute pulmonary edema with an ejection fraction of 25%?

A. Glyburide

B. Metformin

C. Rosiglitazone

D. Exenatide

E. Sitagliptin

Answer: C

DISEASES OF THE ADRENAL GLAND

The adrenal gland is divided into 2 areas: the cortex and medulla.

- **Cortex**
  - **Outer zone** (glomerulosa), the site of aldosterone synthesis
  - **Central zone** (fasciculata), the site of cortisol synthesis
  - **Inner zone** (reticularis), the site of androgen biosynthesis
- **Medulla**

The disorders of hyperfunction of the gland are associated with specific hormones:

- **Cushing syndrome**: increased cortisol
- **Hyperaldosteronism**: increased aldosterone
- **Virilization in women**: increased adrenal androgens

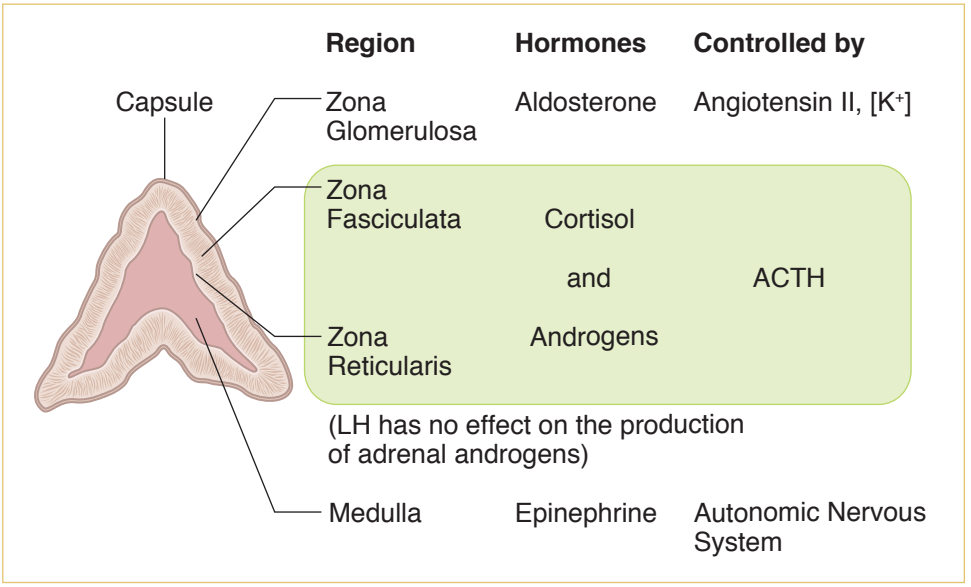


Figure 2-14. Adrenal Cortex Regions

Hyperfunctioning of the Gland

Cushing syndrome

Cushing syndrome results from prolonged exposure to increased cortisol or related corticosteroids. The most common causes are exogenous, iatrogenic, and those secondary to the prolonged use of glucocorticoids. Etiologies include:

- **ACTH-dependent**
  - ACTH-secreting pituitary adenomas (Cushing syndrome)
  - Ectopic ACTH-secreting carcinoma (small cell lung carcinoma, bronchial carcinoid, pheochromocytoma, medullary thyroid carcinoma)
- **ACTH-independent**
  - Adrenal adenoma
  - Adrenal carcinoma

Clinical Findings.

- Deposition of adipose tissue in characteristic sites such as upper fat, moon facies; interscapular buffalo hump; and mesenteric bed, truncal obesity
- Hypertension, muscle weakness, and fatigability related to mobilization of peripheral supportive tissue
- Osteoporosis caused by increased bone catabolism
- Cutaneous striae and easy bruisability

- Acne, hirsutism, oligomenorrhea, and amenorrhea (women) due to increased adrenal androgen secretion
- Glucose intolerance (common, with 20% of patients having diabetes)
- Hypokalemia (due to the mineralocorticoid effect of the steroids; usually not clinically significant) and leukocytosis
- Renal calculi from increased calcium
- Glaucoma
- Increased susceptibility to infections because neutrophils exhibit diminished function as a result of high glucocorticoids

Diagnosis. First-line diagnostic studies include any one of the following tests, but at least 2 of the 3 must be positive.

- **1-mg overnight dexamethasone suppression test** (failure to suppress cortisol to <3)
  - Caution, in the this test can produce falsely abnormal or positive tests, due to the following:
    - Drugs which increase the metabolic breakdown of dexamethasone (e.g., phenytoin, carbamazepine), preventing their ability to suppress cortisol
    - Estrogen use, due to increased production of cortisol binding globulin from the liver
    - Stress (as with starvation, anorexia, alcohol use), which increases glucocorticoid levels
  - If cortisol release is suppressed, the etiology is a pituitary adenoma; check intrapetrosal sinus sampling for ACTH to confirm the pituitary source.
- **Elevated 24-hour urine cortisol level**
- **Elevated late night salivary cortisol level**

Once Cushing is confirmed, the next step is to order an ACTH.

- If ACTH is elevated, it can be a pituitary adenoma or ectopic ACTH-secreting tumor.
  - Confirm the etiology with an MRI of the pituitary. If that is negative, do a high dose dexamethasone suppression test. You give 8 mg of dexamethasone at night and check cortisol in the AM.
  - If high dose does not suppress cortisol production, an ectopic tumor is releasing ACTH.
  - Check chest CT and abdominal CT.
- If ACTH is low, it is an adrenal source, so do an adrenal CT.
  - If ACTH is low, the etiology is most likely from an adrenal tumor (e.g., an adenoma, cancer) or adrenal hyperplasia. When the adrenal gland is the source of increased cortisol production, there is feedback inhibition on the pituitary and the ACTH is suppressed.
  - When ACTH is low, the etiology is confirmed with a CT scan of the adrenals.

Treatment depends on the etiology and can be surgical or medical. Unresectable adrenal tumors are treated with ketoconazole or metyrapone.

Note

A single, random cortisol level is not reliable.

- **High plasma ACTH** suggests a pituitary or ectopic source.
- **Low plasma ACTH** suggests an adrenal tumor or hyperplasia.

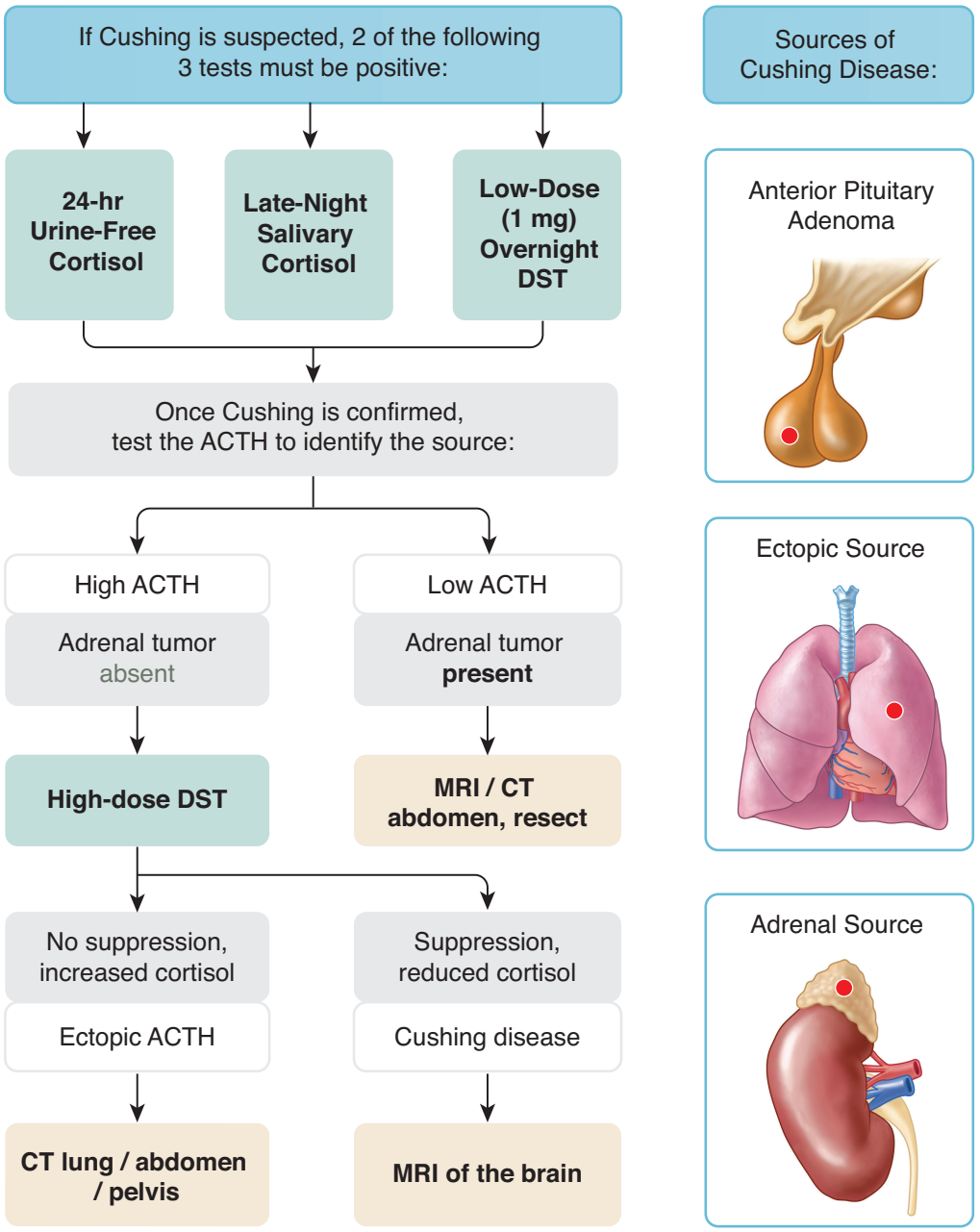


Figure 2-15. Diagnosis and Management for Cushing Syndrome

Hyperaldosteronism

Hyperaldosteronism is associated with hypersecretion of the major adrenal mineralocorticoid, aldosterone. The normal function of aldosterone is to reabsorb sodium and excrete potassium and acid (H^+). There are 2 types of disease:

- **Primary** aldosteronism, in which the stimulus for the excessive aldosterone production is within the adrenal gland
  - Causes include unilateral adrenal adenoma (70% of cases) and bilateral hyperplasia (30%)
  - Excessive black licorice ingestion can mimic this effect, i.e., licorice has aldosterone-like qualities
- **Secondary** aldosteronism, in which the stimulus is extraadrenal
  - Elevated renin level, caused by a low effective circulating volume
  - Seen in renal artery stenosis because there is low blood flow into the JG cells; also seen in cirrhosis and CHF
  - Edema (**high-yield** for the exam)

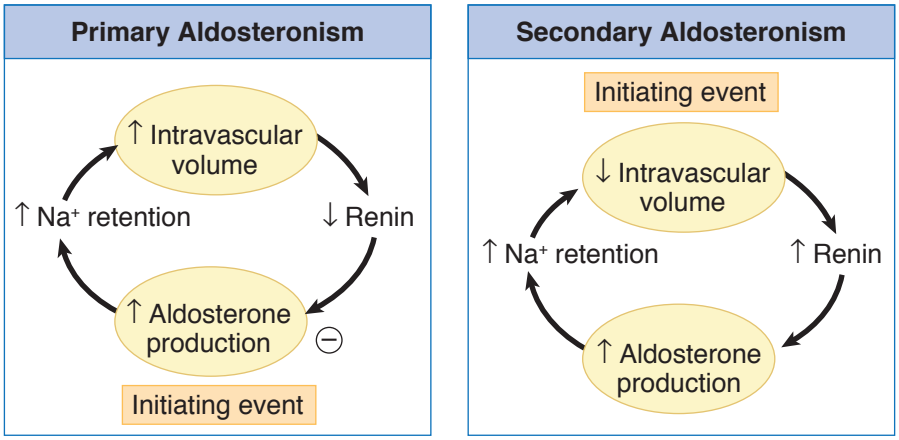


Figure 2-16. Mechanism of Hyperaldosteronism

Clinical Presentation.

- **Primary** hyperaldosteronism
  - Hypertension and low potassium
  - Muscle weakness, polyuria, and polydipsia due to the hypokalemia
  - Metabolic alkalosis due to increased hydrogen ion (H+) excretion (aldosterone causes alkalosis)
  - Edema (rare because of sodium release into the urine)
- **Secondary** hyperaldosteronism
  - Edema and ascites
  - Volume-overload, but the effective circulating volume is low, leading to elevated secretion of renin

Table 2-6. Clinical Findings in Primary and Secondary Aldosteronism

	Primary Aldosteronism	Secondary Aldosteronism
Diastolic hypertension	+	–
Muscle weakness	+	+/–
Polyuria, polydipsia	+	+/–
Edema	–	+/–
Hypokalemia	+	+
Hypernatremia	+	–
Metabolic alkalosis	+	+

Diagnosis.

- Preliminary screen with plasma aldosterone concentration (PAC) and plasma renin activity (PRA): a positive screen is **PAC/PRA ratio >20:1** and **PAC >15 ng/dL**
- Confirmatory screen with an NaCl challenge via normal saline, NaCl tabs, or fludrocortisone: if PAC is still elevated, this confirms the diagnosis
- CT or MRI to evaluate the adrenal glands
- Bilateral adrenal venous sampling (done before surgery even if CT reveals an adrenal mass)
  - Can be an incidental finding, and there may be bilateral adrenal hyperplasia
  - If both adrenal veins have high secretion of aldosterone, do not remove the adrenal mass; the diagnosis is bilateral adrenal hyperplasia and the mass is an incidental finding

Note

Half of patients with primary hyperaldosteronism do not have hypokalemia. Think of this diagnosis when BP is difficult to control or patient is very young.

Bartter syndrome (a cause of secondary hyperaldosteronism without edema or hypertension) results from a defect in the loop of Henle, in which it loses NaCl. The etiology is a defect in the Na-K-2Cl cotransporter. The result is like having a furosemide-secreting tumor. Symptoms include juxtaglomerular hyperplasia, normal to low BP (but no edema), severe hypokalemic alkalosis, defects in renal conservation of sodium or chloride, and renal loss of sodium—all which stimulate renin secretion and aldosterone production.

Treatment.

- Surgical removal for adenomas
- Spironolactone or eplerenone for bilateral hyperplasia, to block aldosterone

Note

Testing can be done on patients who are taking any antihypertensive agent, **except for spironolactone and eplerenone**.

Syndromes of adrenal androgen excess

Syndromes of adrenal androgen excess result from excess production of dehydroepiandrosterone (DHEA) and androstenedione, which are converted to testosterone in extraglandular tissues. The elevated testosterone accounts for most androgenic effects.

Hirsutism, oligomenorrhea, acne, and virilization and common symptoms.

The etiology includes congenital adrenal hyperplasia, adrenal adenomas (rare), and adrenal carcinomas.

Congenital adrenal hyperplasia

Congenital adrenal hyperplasia (CAH) (**most common adrenal disorder of infancy and childhood**) is associated with increased adrenal androgen production due to enzymatic defects. It is the result of autosomal recessive mutations, which produce deficiencies of enzymes needed for cortisol synthesis.

- C-21 hydroxylase deficiency (95% of cases)
- C-11 hydroxylase deficiency: the mineralocorticoid manifestations can be 'biphasic'
  - In early infancy, despite having excessive mineralocorticoid hormones, patients may present with relative 'salt-wasting' (aldosterone deficiency). That is because some infants have inefficient salt conservation as well as immature aldosterone production. During this phase, infants can present with hypotension and hyperkalemia (similar to 21 hydroxylase deficiency).
  - Later in life, there is a better ability to hold onto salt, so patients develop typical C-11 deficiency syndrome (hypertension and hypokalemia).
- C-17 hydroxylase deficiency, characterized by hypogonadism, hypokalemia, and hypertension resulting from increased production of 11-deoxycorticosterone
- Reduced aldosterone secretion (35% of cases)
- Adrenal virilization, with or without an associated salt-losing tendency, owing to aldosterone deficiency, which leads to hyponatremia, hyperkalemia, dehydration, and hypotension

Patients with CAH are female at birth with ambiguous external genitalia (female pseudohermaphroditism), enlarged clitoris, and partial or complete fusion of the labia.

Postnatally, CAH is associated with virilization. Patients may be male at birth with macrogenitosomia; postnatally this is associated with precocious puberty.

Diagnosis. CAH should be considered in all infants exhibiting failure to thrive, especially those with episodes of acute adrenal insufficiency, salt wasting, or hypertension. Testing includes serum testosterone, androstenedione, dehydroepiandrosterone, 17-hydroxyprogesterone, urinary 17-ketosteroid, and pregnanetriol.

Treatment is glucocorticoid (hydrocortisone) replacement.

Clinical Recall

An elderly, obese, diabetic patient presents with LDL 150 mg/dL. Which medication should be given at this time?

A. Niacin

B. Atorvastatin

C. Gemfibrozil

D. Lisinopril

E. Gabapentin

Answer: B

Note

The 'biphasic' presentation is rare. When you think about 11 deficiency, think mineralocorticoid excess (hypertension and hypokalemia) with low cortisol production (remember you need C-11 for the final step in converting to cortisol).

Adrenal incidentaloma

Adrenal incidentaloma is an incidental adrenal mass found on abdominal CT that has been done for an unrelated reason (e.g., abdominal pain). The first step is to determine if it is malignant:

- Irregular borders
- Size >4 cm
- Hounsfield units >10 (hyper density)

If it appears malignant, treatment is surgical removal. If it is benign (smooth borders, <4 cm, <10 HU), treatment is biochemical testing:

- If BP is normal, do a 1 mg dexamethasone suppression test to evaluate for subclinical Cushing syndrome and a 24-hr urine metanephrine and catecholamine test to evaluate for pheochromocytoma.
- If there is hypertension or hypokalemia, do all of the following tests:
  - Plasma aldosterone-plasma renin ratio (to look for primary hyperaldosteronism)
  - 1 mg dexamethasone suppression test (to look for subclinical Cushing syndrome)
  - 24-hr urine metanephrine and catecholamine (to look for pheochromocytoma)

Hypofunctioning of the Gland

Adrenal insufficiency

Note

Half of patients with autoimmune adrenal insufficiency will have other autoimmune disorders, e.g., type I DM, pernicious anemia, celiac sprue, and vitiligo.

Adrenal insufficiency can be divided into primary adrenocortical insufficiency and secondary failure in the elaboration of ACTH.

- **Primary** adrenocortical insufficiency (Addison disease) is a slow, usually progressive disease due to adrenocorticoid hypofunction. The etiology can be secondary to anatomic destruction of the gland (chronic and acute). Autoimmune destruction accounts for 80% of cases.
  - Idiopathic atrophy is the most common cause of anatomic destruction, and autoimmune mechanisms are probably responsible.
  - Anatomic destruction can also be secondary to surgical removal, infection (TB, fungal, cytomegalovirus), hemorrhagic, trauma, and metastatic invasion.
  - Metabolic failure in hormone production can also lead to Addison disease and can be secondary to CAH, enzyme inhibitors, and cytotoxic agents (mitotane).
- **Secondary** adrenal insufficiency is caused by a lack of ACTH from a pituitary source, most commonly an anterior pituitary adenoma.

Note

Adrenal crisis may occur in the following situations:

- Previously undiagnosed patient with adrenal insufficiency who has undergone surgery/serious infection/major stress
- Bilateral adrenal infarction or hemorrhage
- Patient who is abruptly withdrawn from chronic glucocorticoid therapy

Clinical Findings.

- **Primary**: weakness, paresthesias, cramping, intolerance to stress, and personality changes such as irritability and restlessness
  - Chronic disease: small heart; weight loss; sparse axillary hair; hyperpigmentation of the skin (as diffuse brown, tan, or bronze darkening of both exposed and unexposed body parts); arterial hypotension (often orthostatic owing to lack of effect of cortisol on vascular tone); abnormalities of GI function (from mild anorexia with weight loss to vomiting/diarrhea and abdominal pain)
  - Acute disease: fever; hypotension; low sodium with high potassium; mild acidosis

- **Secondary**: similar symptoms to primary, but with the following exceptions
  - No hyperkalemia because ACTH has no control of aldosterone secretion (angiotensin II and serum potassium do)
  - No hyperpigmentation because ACTH levels will be low

In **severe adrenal insufficiency** (adrenal crisis), fever, vomiting, abdominal pain, altered mental status, and vascular collapse may occur.

Diagnosis.

- Rapid ACTH administration and cortisol measurement (obtain cortisol before ACTH)
- WBC count with moderate neutropenia, lymphocytosis, and eosinophilia
- Elevated serum potassium and urea nitrogen
- Low sodium
- Low blood glucose
- Low morning plasma cortisol

Note

A healthy person should show a brisk rise in cortisol level after ACTH administration.

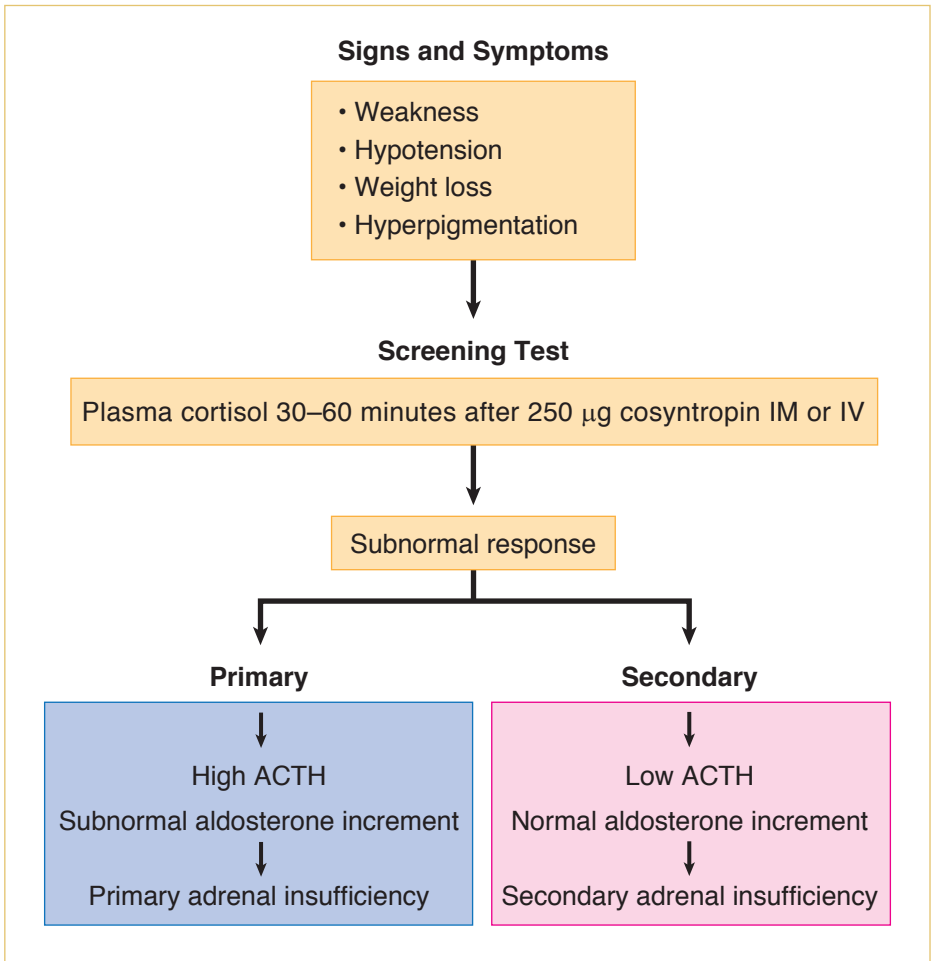


Figure 2-17. Diagnosis of Adrenal Insufficiency

Treatment is hydrocortisone to replace glucocorticoids and fludrocortisone to replace mineralocorticoids (only for primary, not secondary). In high stress states such as sepsis and MI, increase the hydrocortisone dose significantly.

With adrenal crisis, get a cortisol level and then rapidly administer fluids and hydrocortisone.

Note

Remember the **rule of 10%** with pheochromocytoma.

- 10% extraadrenal
- 10% malignant
- 10% in children
- 10% bilateral or multiple (> right side)
- 10% not associated with hypertension

Pheochromocytoma

Pheochromocytoma is a rare, usually benign, tumor that arises from the chromaffin cells of the sympathetic nervous system. It occurs in ~0.1% of the hypertensive population.

- Familial pheochromocytoma (5% of cases) is transmitted as an autosomal dominant trait alone or in combination with MEN type IIa or IIb, von Recklinghausen neurofibromatosis, or von Hippel-Lindau retinal cerebellar hemangioblastomatosis.
- Secretion of dopamine occurs more in familial syndromes and is not associated with hypertension.
- Secretion of epinephrine causes tachycardia, sweating, flushing, and hypertension.
- Norepinephrine is secreted by all extraadrenal tumors.

Clinical Findings.

- Paroxysms or crisis (>50% of patients)
- Headache, profuse sweating, palpitations, and apprehension (common)
- Pain in the chest or abdomen, associated with nausea/vomiting
- Elevated BP with tachycardia in crisis (40% of patients have elevated BP only during the attack and 60% have stable hypertension)
- Anxiety, tremor
- Weight loss
- Orthostatic hypotension
- Mild hyperglycemia (30% of patients)
- Death prior to diagnosis, often due to cardiac arrhythmia and stroke (>33% of cases)

Characteristic lesions include:

- **Adults:** unilateral, solitary lesion (80%) with 10% bilateral and 10% extraadrenal
  - Solitary lesions favor the right side.
  - Extraadrenal pheochromocytomas are mostly located within the abdomen and near the celiac, superior mesenteric, and inferior mesenteric ganglia.
- **Children:** 25% bilateral and 25% extraadrenal

Diagnosis is made with the following testing:

- **When pre-test probability is low** (e.g., lack of symptoms or adrenal mass without typical [e.g., vascular] radiographic findings): 24-hour urinary catecholamines, metanephrines, VMA
- **When clinical suspicion is high:** plasma metanephrine (but false-positives are common)
- **Best test overall:** 24-hour urinary metanephrines
- If catecholamines or metanephrines are abnormal, confirm the tumor with CT or MRI; if location of pheochromocytoma is still not revealed, do an MIBG scan

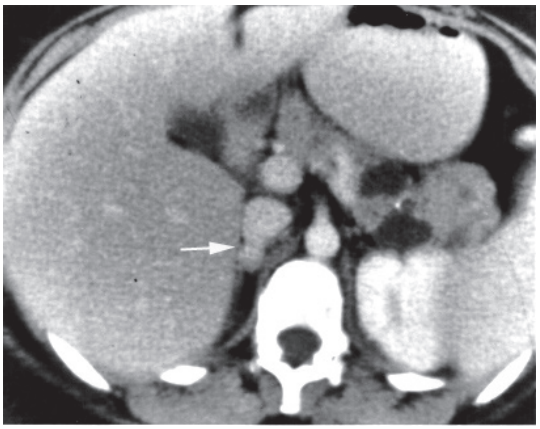


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Figure 2-18. Pheochromocytoma

The differential diagnosis of pheochromocytoma includes essential hypertension, anxiety attacks, factitious crisis, intracranial lesions, and autonomic epilepsy.

Treatment.

- Alpha-adrenergic blockade, phentolamine, and/or phenoxybenzamine to control BP and prevent a hypertensive crisis (since high circulating catecholamine levels stimulate alpha receptors on blood vessels and cause vasoconstriction)
- Beta blockers if significant tachycardia occurs after alpha blockade
  - Do not give beta blockers until adequate alpha blockade has been established, since unopposed alpha-adrenergic receptor stimulation can precipitate a hypertensive crisis.
  - Noncardioselective beta blockers (propranolol, nadolol) are the usual choice, though cardioselective agents (atenolol, metoprolol) may be used.
  - Labetalol has been associated with paradoxic episodes of hypertension; thought to be secondary to incomplete alpha blockade.
- Surgical removal of the pheochromocytoma (curative) only after BP has been stabilized; to control BP during surgery, use IV phentolamine—a rapid-acting alpha-adrenergic antagonist.

DISEASES OF THE TESTES

Hypogonadism

In hypogonadism there is decreased function of the testes or ovaries, resulting in the absence or impairment of secondary sexual characteristics and infertility.

- **Primary hypogonadism** (hypergonadotropic: increased LH, FSH) can be caused by:
  - Klinefelter syndrome (small testes, eunuchoid, 47XXY)
  - Anorchia
  - Surgical/accidental castration or radiotherapy
  - Infections (mumps, TB, leprosy)
  - Chemotherapeutic agents (cyclophosphamide)

- **Secondary hypogonadism** (hypogonadotropic: decreased LH, FSH) can be caused by:
  - Hypopituitarism secondary to idiopathic causes or tumors
  - Hypothalamic lesions
  - Kallmann syndrome (hypogonadic hypogonadism, associated with decreased sense of smell)
  - Chronic use of opiates, anabolic steroids, or glucocorticoids
  - Infiltrative diseases (hemochromatosis)
  - Sleep apnea

Clinical Findings.

- Prepubertal hypogonadism, usually caused by a specific gonadotropic deficiency of the pituitary
- Underdeveloped external genitalia, high-pitched voice, beard that does not grow, lack of libido and potency
- Possible gynecomastia
- Possible testes absent from scrotum
- Retarded bone age
- Low to normal urinary 17-ketosteroid and below-normal serum testosterone
- Fatigue, weakness, poor libido, erectile dysfunction (adults)
- Increased risk of osteoporosis (men); treatment is testosterone

Klinefelter syndrome is the most common primary developmental abnormality causing hypogonadism (testicular damage), affecting 1 of every 400–500 males. It is caused by one or more supernumerary X chromosomes.

- 47,XXY karyotype (80% of patients)
- Gynecomastia, with elevated LH and FSH
- Sterility and lack of libido
- Small and thin testes
- Possible intellectual disability
- Low-normal or normal urinary 17-ketosteroids; low to normal serum testosterone; elevated LH and FSH; and elevated serum estradiol
- Affected males have 20× increased risk of breast cancer

Diagnosis.

- Check total testosterone at 8 AM; if it is low, must repeat to confirm
  - Two low AM total testosterone tests are required to diagnose hypogonadism
  - PM total testosterone tests are inaccurate.
- If testosterone is low, check LH next.
  - If **LH is elevated**, it is primary hypogonadism. (Due to negative feedback inhibition, LH must be elevated in primary hypogonadism.)
  - If **LH is low or normal** (abnormally normal), it is secondary hypogonadism. Check prolactin next (prolactin can suppress GnRH, leading to low LH). If prolactin is elevated, do pituitary MRI.

Note

- For diagnosing hypogonadism, neither PM total testosterone nor free testosterone is a correct diagnostic test. (Also, free testosterone has a short half-life.)
- However, free testosterone is the correct diagnostic test (only) for an obese man with 2 low AM total testosterone values. (Obesity has low SHBG, which can produce a false low total testosterone, so check free testosterone to confirm hypogonadism.)

- If patient has arthralgia and elevated liver enzymes, check iron studies for hemochromatosis.

Treatment is testosterone replacement.

- Monitor hematocrit to screen for polycythemia.
- Monitor PSA to screen for prostate cancer.
- Side effects of testosterone replacement are increased risk of venous thromboembolism (due to erythrocytosis) and potential increased risk of cardiovascular disease.

Clinical Recall

Which of the following tests is most specific in the diagnosis of pheochromocytoma?

A. Urinary-free catecholamines with plasma catecholamine

B. 24 hour urinary VMA with free catecholamines

C. Urinary VMA with plasma catecholamine

D. Plasma catecholamines and VMA with urinary VMA and catecholamine

E. Plasma metanephrine with 24 hour urinary metanephrine and VMA

Answer: E

Note

If LH is not elevated, it is not primary hypogonadism.

Rheumatology 3

Learning Objectives

- ❑ List the steps for evaluating a patient with arthritis
- ❑ Differentiate the types of arthritis
- ❑ Describe the treatment approaches to rheumatoid arthritis, systemic lupus erythematosus, drug-induced lupus, scleroderma, Sjögren syndrome
- ❑ Describe the treatment approaches to seronegative arthropathies, including ankylosing spondylitis, reactive arthritis, psoriatic arthritis, and enteropathic arthritis
- ❑ Answer questions about the management of osteoarthritis, crystal-induced arthropathies, and septic arthritis
- ❑ Describe the diagnosis and management of vasculitis syndromes and inflammatory myopathies

TESTS FOR RHEUMATOLOGIC DISEASE

Joint Aspiration (Arthrocentesis)

Fluid in the joint requires immediate analysis. The basic tests to run on the synovial fluid are as follows:

- The 3 Cs (**cell count, crystals, and cultures**)
- The **Gram stain**

Synovial fluid may be stratified according to the number of cells:

- **OA and traumatic arthritis**: 200–2,000 WBCs/mm^3 in synovial fluid
- **Inflammatory diseases** (RA, gout): 5,000–50,000 WBC/mm^3
- **Septic arthritis**: >50,000 WBC/mm^3

Note

The white cells counts in the synovial fluid are just a guide. One can see septic joints with <50,000 PMNs, and in other cases, crystal-induced arthritis with >50,000 PMNs.

Table 3-1. Synovial Fluid Analysis in Rheumatologic Disease

Disease	WBCs	Crystals/Polarization
DJD	<2,000	Negative traumatic
Inflammatory	5,000–50,000	• Gout: needle-shaped, negative birefringent • Pseudogout (CPPD): rhomboid-shaped, positive birefringent
Septic	>50,000	Negative (Gram stain and culture usually negative for GC but positive in *Staph*, strep, and gram-negatives)

There are a few exceptions:

- Septic arthritis can be present with <50,000 WBC/mm^3 in the joint aspirate if antibiotics are given beforehand. Consider it if >5,000 WBC/mm^3 in the synovial fluid and monoarticular arthritis, but there is an absence of crystals.
- Gout and pseudogout uncommonly present with >50,000 WBC/mm^3 in the absence of infection. Consider them if there is evidence of crystals in the aspirate.
- Culture of joint fluid is positive in only ≤50% of gonococcal arthritis cases.

Antinuclear Antibodies

Antinuclear antibodies (ANAs) are antibodies with the capability to bind to certain structures within a cell nucleus. They are typically found in patients whose immune system is predisposed to generating antibodies against their own body tissues (called *autoimmunity*), such as SLE, Sjögren syndrome, and systemic sclerosis. However, they are also found in ~5% of healthy people (though usually in low titers [<1:80]).

The ANA test is performed by exposing the antibodies in the serum of the blood to the laboratory test cells. It is then determined whether there are antibodies that react with various parts of the nucleus.

Subsets of ANAs are associated with specific autoimmune diseases and thus used to further diagnose those diseases. For example, anti ds-DNA and anti-SM antibodies are found in patients with SLE; anti-histone antibodies are found in patients with drug-induced lupus.

Table 3-2. Specific ANAs

Anti-dsDNA (native DNA)	SLE only (60%); an indicator of disease activity and lupus nephritis
Anti-SM	SLE only (25–30%)
Anti-histone	Drug-induced lupus (95%)
Anti-Ro (SSA)	Neonatal lupus, Sjögren and in the 3% of ANA-negative lupus
Anti-LA (SSB)	Sjögren
Anti-centromere	CREST
Anti-RNP	100% mixed connective tissue disease (MCTD)

Rheumatoid Factors

Rheumatoid factors (RFs) are autoantibodies against the Fc portion of IgG.

- Found in ~70% of patients with RA although they are not specific for RA
- Found in 5% of healthy adults (prevalence increases with age, i.e., up to 20% in those age >65)

While RFs are neither sensitive nor specific for the diagnosis of RA, their presence can be of prognostic significance: patients with **high titers** tend to have **more aggressive disease with extraarticular manifestations**.

Antineutrophil Cytoplasmic Antibodies

Antineutrophil cytoplasmic antibodies (ANCAs) are antibodies directed against certain proteins in the cytoplasm of neutrophils.

- **Cytoplasmic (c) ANCA** is the diffuse staining pattern observed when serum antibodies bind to indicator neutrophils; it is seen in >90% of patients who have granulomatosis with polyangiitis.
- **Perinuclear (p) ANCA** is a localized staining pattern observed on the indicator neutrophils (the major target of these antibodies is the enzyme myeloperoxidase); it is found in PAN and Churg-Strauss (known as eosinophilic vasculitis) but is a nonspecific test.

Clinical Correlate

Overall, >95% of SLE patients have positive ANA test results, making a negative ANA result a good rule-out test for SLE.

Interpret a positive ANA test in the context of the clinical symptoms:

- Positive ANA with no symptoms or abnormal tests is likely to be a false–positive (5% of population)
- Positive ANA with arthritis, proteinuria, and pleural effusion is likely to be associated with SLE

Antiphospholipid Antibody Syndrome

Antiphospholipid antibody syndrome (lupus anticoagulant or anticardiolipin antibodies) is a hypercoagulable state associated with a group of antibodies that are directed against phospholipids or cardiolipins.

- Etiology unclear, i.e., not clear if the antibodies are directly involved in the etiology of the clotting disorder associated with this syndrome
- The nature of these antibodies causes the common lab abnormalities associated with the syndrome, i.e., elevated PTT and false-positive RPR or VDRL

Clinically, it presents with spontaneous abortion in otherwise healthy women or thromboembolism (pulmonary embolism, DVT) in other patients.

Two first-trimester spontaneous abortions suggest antiphospholipid antibodies.

ARTHRITIS

Initial Evaluation

When a patient presents with joint swelling, a differential diagnosis is generated based on the answers to the following questions:

Note

Do not go further into a history unless these questions have been answered.

1. **What is the distribution of joint involvement and how many joints are involved?**
   - Polyarticular symmetric involvement is seen with RA, SLE, parvovirus B19, hepatitis B, and vasculitis.
   - Monoarticular arthritis is consistent with OA, crystal-induced arthritis (gout, pseudogout), septic arthritis (gonococcus), trauma, and hemarthrosis.
   - Migratory arthropathy (inflammation and pain migrate from joint to joint while the previous involved joints improve) is caused by rheumatic fever, disseminated gonococcal infection, and Lyme disease.
   - Oligoarticular asymmetric arthritis is common with the spondyloarthropathies (ankylosing spondylitis) and OA involving the small joint of the upper extremities; it is rarely in the presentation of polyarticular gout.
2. **Are the symptoms acute or chronic?**
   - OA is a chronic disease; patients have symptoms for months to years.
   - With septic arthritis or crystal-induced arthropathy, patients have short-lived symptoms, i.e., only a few days.
3. **Does the patient have systemic symptoms (beyond the arthritis)?**
   - SLE presents with lung (pleural effusions), kidney (proteinuria and renal failure), CNS (vasculitis, strokes, and change in personality), skin (malar and photosensitivity rash), and hematologic (immune-mediated anemia, thrombocytopenia) manifestations.
   - Sjögren syndrome has keratoconjunctivitis sicca (dry eyes/mouth) and parotid enlargement.
   - Systemic sclerosis has skin involvement and Raynaud phenomenon.

- Wegener granulomatosis presents with upper respiratory (sinusitis and rhinitis), lower respiratory (lung nodules and hemoptysis), and renal (necrotizing glomerulonephritis) involvement.
- OA has no systemic symptoms.

4. Is there evidence of joint inflammation?

- Evidence of joint inflammation includes joint stiffness in the AM >1 hour, joint erythema and warmth, and elevated ESR and C-reactive protein.
- RA would produce inflammation, while OA would not.

Examples of patients presenting with joint swelling include:

- A 62-year-old man presents with right knee pain
- A 24-year-old woman presents with bilateral wrist, MCP, PIP joint swelling, and pain
- A 32-year-old man returns to your office with knee swelling after being seen a week ago for left wrist pain and swelling, which has now resolved
- A 29-year-old man has right knee pain and swelling and left hip pain

Rheumatoid Arthritis

A 26-year-old woman with no prior medical history presents with a 3-week history of joint swelling and stiffness. Every morning she has stiffness for about 2 h, but that improves as the day progresses. She denies back stiffness or back pain. She has fatigue and low-grade fever. On examination of the wrist, MCPs and PIPs are red and swollen on both hands. The DIPs are not involved. There is fluid in the wrist joints. Otherwise the examination is normal.

Rheumatoid arthritis (RA) is a chronic inflammatory multisystemic disease with the main target being the synovium.

- Women > men by 3:1
- Onset is most commonly age 35–50
- Etiology is unknown
  - RA may be triggered as a reaction to an infectious agent (mycoplasma, parvovirus) in a susceptible host.
  - Of the environmental factors, only cigarette smoking seems to be associated with RA.

Symptoms include:

- Inflammatory synovitis (**hallmark of RA**), presenting in a symmetric distribution
  - First, an initiation phase of nonspecific inflammation
  - Next, an amplification phase, resulting from T-cell activation
  - Last, the chronic inflammation and tissue injury phase
- Intense joint inflammation, with the potential to destroy cartilage, cause bone erosions, and eventually deform the joint
- Positive anti-CCP (cyclic citrullinated peptide) (**very high specificity**)

The predominant infiltrating cell is the T lymphocyte. Diseases such as HIV, where T cells are decreased, will characteristically improve preexisting RA; this also explains why RA is very rare in patients with HIV.

Clinical Presentation. Required for a diagnosis of RA are 4 of the following diagnostic criteria:

- Morning stiffness (>1 h) for 6 weeks
- Swelling of wrists, MCPs, PIPs for 6 weeks
- Swelling of 3 joints for 6 weeks
- Symmetric joint swelling for 6 weeks
- RF positive or anti-cyclic citrullinated peptide
- CRP or ESR

X-ray abnormalities and nodules are not needed for diagnosis.

Note

DIPs and joints of the lower back are never involved in RA.

Criteria. RA is a chronic inflammatory symmetric arthropathy. There needs to be involvement of multiple joints, but some joints are **never** involved in RA:

- DIPs
- Joints of the lower back

Note

In 2010, new criteria for RA were proposed by the American College of Rheumatology and European League against Rheumatism focusing more on serology, acute phase reactants, number of joints involved, and duration of joint involvement over 6 weeks. This leads to a point system.

For the moment, the 1987 criteria are not obsolete.

Because RA is a systemic disease, ~70% of patients present with constitutional symptoms—fatigue, anorexia, weight loss, generalized weakness—before the onset of the arthritis.

- Damage to the ligaments and tendons
  - Radial deviation of the wrist with ulnar deviation of the digits
  - Boutonnière deformity
  - Swan-neck deformity
- Rheumatoid nodules
  - Initial event caused by focal vasculitis
  - 20–30% of patients with RA; usually occur in areas of mechanical stress (olecranon, occiput, Achilles tendon)
  - Methotrexate may flare this process
- Felty syndrome (RA + splenomegaly + neutropenia)
- Caplan syndrome (RA + pneumoconiosis)
- RF or anti-CCP
- Anemia
- ESR or C-reactive protein
- Synovial fluid analysis

Note

RF can cause elevated an cryoglobulin level.

Diagnosis. Diagnosis is clinical; there is no single test that will diagnose RA.

Anti-CCP is more specific than RF.

Treatment.

- NSAIDs
  - In RA, NSAIDs are not "better" than aspirin but they have fewer GI side effects
  - All NSAIDs are equally effective, even the newer ones
  - Cyclooxygenase 2 (COX-2) inhibitors have fewer side effects (less GI disturbance)
  - Do not use NSAIDs with steroids
- Hydroxychloroquine and sulfasalazine for early, mild disease
- Glucocorticoids (short courses only, while waiting for methotrexate to work)
- **Disease-modifying agents**
  - Methotrexate (MTX) (**gold-standard**)
    - If MTX does not control disease, add an anti-TNF medication
  - Tumor necrosis factor (TNF) receptor inhibitors
    - Infliximab, a monoclonal antibody to TNF-α that binds to TNF-α in the joint and circulation. The combination of infliximab + methotrexate is very effective in reducing clinical manifestations of disease. Infliximab is given as an IV infusion.
    - Adalimumab, an anti-TNF mAb that differs from infliximab in that its sequences are entirely human
    - Etanercept, a human fusion protein that is entirely human; anti-etanercept antibodies are relatively uncommon
    - Newer biologics
    - Side effects include sepsis, disseminated TB (always assess for TB beforehand), and other opportunistic infections
  - Antimalarials
  - Gold
  - Sulfasalazine

Table 3-3. Side Effects of DMARD

Drug	Profile/Side Effects	Screening Tests for Toxicity
Hydroxychloroquine	Retinopathy	Regular eye examination
MTX (methotrexate; most utilized agent and mainstay of treatment)	Rapid onset of action; hepatitis and hepatic fibrosis; pneumonitis; may flare rheumatoid nodules	CBC and liver enzymes every 4–8 weeks

Note

Recent studies have shown that excessive amounts of the pro-inflammatory cytokines, TNF-a, IL-1, and IL-6, mediate most of the pathogenic features of RA. This underscores the focus of new treatment modalities on inhibiting these cytokines.

Clinical Correlate

COX-2 inhibitors are a type of NSAID which selectively block the COX-2 enzyme at the site of inflammation. Their benefit is that they do not inhibit COX-1 (an enzyme that helps with the production of the protective stomach lining). Traditional NSAIDs block both COX-1 and -2, which can lead to increased risk of GI side effects.

Note

- Tumor necrosis factor alpha (TNF-α) is a pro-inflammatory cytokine produced by macrophages and lymphocytes. It is found in large quantities in the rheumatoid joint and is produced locally in the joint by synovial macrophages and lymphocytes infiltrating the joint synovium.
- TNF inhibitors relieve the signs/symptoms of RA, slow/halt radiographic damage, and are proven effective for those who are resistant to MTX.

Aggressive disease is likely to occur with the following features: high titers of RF, diffuse rheumatoid nodules, early joint erosions, late age of onset, and certain subtypes of the HLA-DR4.

Note

Because of the increased risk of MI, both rofecoxib and valdecoxib have been recalled; currently only celecoxib is available.

Complications of RA include:

- Atlantoaxial subluxation may occur with excessive movement at the junction between the atlas (C1) and axis (C2), due to a bony or ligamentous abnormality. (In RA, the incidence of cervical involvement is 25–80% and results from pannus formation at the synovial joints between C1 and C2.)
- Neurologic symptoms may occur when the spinal cord is involved (paraplegia, quadriplegia). Commonly, patients have subtle symptoms, i.e., neck pain (occipital), C2 radicular pain (paresthesias of the hands and feet), and myelopathy. Consider this diagnosis in patients who have RA and neck pain, paresthesias, etc. The first diagnostic test is x-ray of the cervical spine (multiple views, including an open-mouth view), and possibly CT scan or MRI. If radiologic testing is positive, refer to a spine surgeon. Before any intubation or anesthesia, use x-ray to screen all RA patients for C1–C2 subluxation.
- A swollen painful calf may occur, as a possible ruptured Baker cyst. Baker cyst is the extension of inflamed synovium into the popliteal space.

Note

Screen for TB before using TNF inhibitors.

Clinical Pearl

Consider atlantoaxial subluxation in patients with RA who complain of occipital headaches and upper extremity tingling and numbness.

Always rule out subclinical subluxation in patients with RA who are undergoing surgery and intubation electively.

Clinical Recall

A 39-year-old woman presents with pain and stiffness in her hands and wrists for 6 weeks. She is diagnosed with rheumatoid arthritis, although there is no evidence of erosion on x-ray. Which of the following is the best management at this time?

A. NSAID alone

B. NSAID and corticosteroids

C. Corticosteroids alone

D. Corticosteroids and methotrexate

Answer: A

Osteoarthritis

A 64-year-old man presents with knee pain. He tells you that he has had right knee pain for many years but it has recently gotten worse. He denies constitutional symptoms and other joint pain except for his left second and third DIPs. He has not noticed stiffness in the morning. On examination crepitations are heard as you move the right knee, but otherwise there is no evidence of swelling, warmth, or erythema of the knee. Laboratory testing is unremarkable.

Osteoarthritis (OA) is the most common joint disease in humans; the target tissue is articular cartilage. There is destruction of cartilage along with secondary remodeling and hypertrophy of the bone.

Unlike RA, OA is not an inflammatory disease.

- Knee OA is the leading cause of chronic disability in the elderly.
- Major risk factors for OA include age, female sex, genetic factors, major joint trauma, repetitive stress, and obesity.
- Classification: **idiopathic** (most common form) where no predisposing factor is evident, and **secondary**, where there is an underlying cause, e.g., another arthropathies (gout), endocrine disease (DM, acromegaly), deposition diseases (hemochromatosis), and mechanical factors (valgus or varus deformity, unequal lower extremity length).
  - Any disease that causes stress or trauma to a joint may eventually cause secondary OA.
  - Idiopathic OA and secondary OA are pathologically indistinguishable.

The most common joint affected by OA is the knee, and the second most common is the base of the thumb.

Clinical Presentation. The major joints involved in OA are the weight-bearing joints (hip and knee) and the small joints of the fingers (PIPs and DIPs). These joints are affected in an oligoarticular-asymmetric or monoarticular pattern. The joint involvement is very slow, progressive, and irreversible. Because the cartilage fails and there is increased pressure on articular bone, joint pain increases with exercise and is relieved by rest. Morning stiffness is always <20–30 min. Crepitations may be noted with movement of the joint. There are no systemic manifestations in OA.

- Lab tests are always normal, especially indices of inflammation.
- Thus, ESR and C-reactive protein are always normal. (If ESR is elevated, some other process is complicating OA, e.g., septic joint, or it is not OA.)
- X-ray findings include osteophytes and unequal joint space.
- Osteophytes (spurs) are the reparative efforts by the bone; when these occur in the PIPs they are called Bouchard's nodes, whereas similar changes occurring in the DIPs are called Heberden's nodes.

Diagnosis is made with clinical and x-ray findings.

Treatment. There is no cure for OA, so focus on maintaining mobility and reducing pain. Therapy is palliative because no agent has been shown to change the natural course of the disease.

- Reduce joint loading with correction of poor posture and weight loss.
- Design physical therapy and exercise programs which maintain range of motion, strengthen periarticular muscles, and improve physical fitness.
- Use NSAIDs only to alleviate pain (chondroprotective effect of certain NSAIDs has not been proven). In double-blinded placebo trials, there was no difference in relief of joint pain among acetaminophen (4,000 mg/d), analgesic doses of ibuprofen (1,200 mg/d), and antiinflammatory doses of ibuprofen (2,400 mg/d).

Note

Acetaminophen is effective if given as a standing medication.

- Do not exceed 4 grams per day (3 grams in the elderly).
- Do not exceed 2 grams per day in those with liver dysfunction.

- Use acetaminophen as the first drug to use for pain in OA. However, it is reasonable to add analgesic doses of NSAIDs if there is no relief. Use cautious dosing with the elderly because they are at highest risk for the side effects associated with NSAIDs, especially GI (ulcers, hemorrhage, etc.). Consider COX-2 inhibitors for those at high risk for GI complications (only available agent is celecoxib).
- Use capsaicin cream, which depletes local sensory nerve endings of substance P. Some patients do feel local burning.
- Perform orthopedic surgery and joint arthroplasty only when aggressive medical treatment has been unsatisfactory, especially if the patient's quality of life has been decreased.
- Intraarticular injection of hyaluronic acid has been approved for treatment of knee OA that hasn't responded to pharmacologic treatment. However, its effectiveness has been questioned since a large clinical trial failed to demonstrate superiority over intraarticular injections of saline. Similarly, glucosamine and chondroitin sulfate are not routinely used for OA since they have not been shown to be more effective than placebo. There is ongoing research to examine whether glucosamine is chondroprotective.

Note

There are rare cases of erosive OA, polyarticular OA, and OA with inflammatory features. You will not need to know them for the exam.

Clinical Recall

Which of the following is a major risk for osteoarthritis?

A. Onset at early age

B. Male gender

C. Long-term steroid use

D. Low BMI

E. Trauma

Answer: E

SYSTEMIC LUPUS ERYTHEMATOSUS

A 35-year-old woman is brought for the evaluation of confusion lasting 1 day. Her friends and family inform you that "she did not know how to come home from work" and that lately "she has not been herself." You find that the patient has elevated blood pressure, decreased air entry on the right lung base with dullness to percussion, and symmetrical joint swelling of the wrists and MCPs. Chemistry profile shows elevated creatinine 2.4 mg/dL and protein in the urine on the urinalysis.

Systemic lupus erythematosus (SLE) is a systemic disease in which tissues and multiple organs are damaged by pathogenic autoantibodies and immune complexes. Etiology is unknown.

- 90% of cases are women.
- The abnormal immune response probably depends on interactions between a susceptible host and environmental factors. **Ultraviolet (UV)-B light** is the only environmental factor known to cause flares.

Clinical Presentation. Required for a diagnosis of SLE are 4 of the following diagnostic criteria:

- Malar rash
- Discoid rash
- Photosensitivity
- Oral ulcers
- Arthritis
- Serositis (pleuritis or pericarditis)
- Renal involvement
- Neurologic disorder (seizures or psychosis)
- Hematologic disorder (hemolytic anemia, leukopenia, thrombocytopenia)
- Immunologic disorder (anti-dsDNA, anti-SM, and other ANAs)

Summary of Criteria

- Arthritis is identical to that of RA except that it is non-erosive.
- Both the malar rash and photosensitivity rash (diffuse, maculopapular) flare with exposure to UV-B light (thus are considered photosensitive) and resolve with no scarring of the skin. The discoid lupus (DLE) is a circular rash with a raised rim that occurs over the scalp and face; it can be disfiguring because of central atrophy and scarring. Only 5% of patients with DLE will go on to develop SLE.
- All patients with renal involvement must undergo renal biopsy before treatment is initiated.
- Change of personality and psychosis may be manifestations of CNS lupus. Seizures, paralysis, and aphasia may follow.
- Libman-Sacks endocarditis is a noninfectious endocarditis that is occasionally seen in lupus patients.

Diagnosis. A positive ANA supports the diagnosis but is not specific for SLE. Complement levels (C3, C4) are decreased in those with active lupus, as are elevated levels of ds-DNA antibodies.

Treatment. There is no cure; treat to control symptoms.

- NSAIDs to treat arthritis and pleurisy
- Corticosteroid creams to treat skin rash; antimalaria drugs (hydroxychloroquine) and oral corticosteroids for skin and arthritic symptoms

- Cytotoxic drugs (azathioprine, cyclophosphamide, and mycophenolate) for severe symptoms (lupus nephritis, heart and lung involvement, hemolytic anemia, CNS involvement), along with corticosteroids
- Mycophenolate to treat lupus nephritis

All patients should be advised to wear protective clothing, sunglasses, and sunscreen when in the sun. Belimumab is an inhibitor of B-cell activation; it is an IgG monoclonal antibody given intravenously to prevent B-cell activation.

Prognosis. The prognosis of patients with SLE has improved significantly in recent years with a 10-year survival rate >85%. People with severe involvement of the CNS, kidney, heart, and lungs have a worse prognosis in terms of overall survival and disability. Lupus nephritis is probably the most common cause of disability in patients with SLE.

Note the following with respect to **SLE** and **pregnancy:**

- Fertility rates are normal in patients with SLE, but spontaneous abortion and stillbirth are more common when compared with healthy patients; one reason for the spontaneous abortion may be anti-phospholipid antibodies, which cause placental infarcts. This is treated with low-molecular weight heparin during pregnancy.
- It is unclear whether lupus worsens with pregnancy. In the case of a lupus flare during pregnancy, steroids may be used safely to suppress the disease.
- All pregnant patients with lupus need to be screened for SSA/anti-Ro antibodies. These antibodies cross the placenta and are passively transferred to the fetus, causing neonatal lupus and heart block.

DRUG-INDUCED LUPUS

Drug-induced lupus erythematosus is a side effect of certain medications. Over 40 drugs have been implicated, but the most common are hydralazine, isoniazid, procainamide, and quinidine.

Symptoms typically include arthritis, fatigue, fever, and pleurisy (rare).

- Acute onset SLE is usually not confused with drug-induced lupus, due to the lack of skin disease, kidney disease, and milder symptoms seen in the latter. Also, photosensitivity, hair loss, and CNS disease are uncommon in drug-induced lupus.
- Patients with drug-induced lupus develop ANAs, although those with drug-induced lupus related to quinidine often are ANA-negative. The ANAs in drug-induced lupus are autoantibodies that react with a histone-DNA complex, which is the major component of the nucleus (anti-histone antibodies).

Note

Drug-induced lupus usually spares the visceral organs (kidney, CNS and heart).

Diagnosis is anti-histone antibody testing, a sensitive marker this disease. (Hydralazine is the exception, as only 35% of patients will have positive anti-histone antibodies.)

Treatment is to stop the suspected medication. Resolution of symptoms in 1–2 weeks will confirm the diagnosis.

SCLERODERMA

A 36-year-old woman presents with skin tightness and painful fingertips with exposure to cold for >1 year. Physical examination reveals blood pressure 165/100 mm Hg and diffuse shiny, thickened skin. Lab tests reveal elevated serum creatinine. The examination is otherwise normal.

Systemic sclerosis (SSc) (or scleroderma) is a chronic multisystem disease characterized by a thickening of the skin caused by accumulation of connective tissue and by involvement of visceral organs (GI, lungs, kidneys).

SSc comes in diffuse and limited forms. Diffuse scleroderma is more likely to affect internal organs. Limited scleroderma affects part of the body and a slower progression.

Clinical Presentation. All patients with SSc have the following symptoms, but there are differences in the severity and distribution of the disease.

- Skin thickening
- Esophageal disease
- Lung disease
- **Raynaud phenomenon**, episodes of pallor or cyanosis in response to cold or emotional stimuli, as a result of vascular damage and diminished blood flow to the extremities; after rewarming the hands, the blood flow will rebound (hyperemia) and the skin will appear reddened or blushed
  - Pallor is caused by vasoconstriction of blood vessels (arteries and arterioles) that results in reduced blood flow
  - Cyanosis is created by deoxygenation of slow-flowing blood
  - Patients complain of cold sensitivity and involvement of other areas of the skin, including the ears, nose, and lower extremities
  - Episodes come as sudden attacks and are often triggered by rapid changes in ambient temperature; attacks may begin in 1 or 2 fingers but typically involve all fingers and/or toes symmetrically and bilaterally
  - In **primary Raynaud phenomenon** (Raynaud disease), the patient has no associated underlying disease, while in **secondary Raynaud phenomenon**, the patient has a defined secondary or associated disease (e.g., scleroderma).
    - To differentiate them, do a nailfold capillaroscopy test (place a drop of oil on patient's nailfold at the base of the fingernail).
    - Examine that area under a microscope for any capillary changes.
  - Enlarged, dilated, or absent nailfold capillaries are noted among patients with scleroderma and other autoimmune diseases.
- Positive ANA testing

Note

Raynaud phenomenon

- Seen in 5% of the general population, especially young women
- About 30% have a first-degree relative with Raynaud
- Most patients have primary Raynaud phenomenon without any defined cause or associated systemic disease

Additional symptoms of the **diffuse form** include:

- GI: esophageal dysmotility; hypomotility of small intestine with bacterial overgrowth and malabsorption; dilatation of large intestine with formation of large diverticula
- Pulmonary: pulmonary fibrosis with restrictive lung disease, pulmonary hypertension, alveolitis, and cor pulmonale
- Renal: scleroderma renal crisis in which malignant hypertension develops and causes acute renal failure (had been leading cause of death but is now easily treated with ACE inhibitors)
- Cardiac: myocardial fibrosis, pericarditis, valve disease, arrhythmias due to fibrosis of the conducting system

Note

Pulmonary involvement is now the leading cause of death in SSc.

Additional symptoms of the **limited form** include:

- Skin involvement that does not extend above the elbow or above the knee (rarely, the face may be affected)
- Pulmonary arterial hypertension is more common than interstitial fibrosis
- Positive ANA test, showing a pattern of anticentromere antibodies (up to 90% of patients)
- Negative antibodies to Scl-70, as compared with positive antibodies to Scl-70 with diffuse scleroderma

An important complication of SSc is **scleroderma renal crisis,** when malignant hypertension occurs over days to weeks. It is associated with acute renal failure (rapid rise in creatinine and proteinuria). Treatment is ACE inhibitors (enalapril, lisinopril), initiated immediately.

Limited scleroderma was previously called **CREST syndrome**. The acronym CREST represents the hallmarks of the disease:

- **C**alcinosis (calcium deposits in soft tissues–usually fingers, especially PIP joints), knees, elbows; deposits occur near skin surface and may ulcerate and become infected)
- **R**aynaud
- **E**sophageal dysfunction
- **S**clerodactyly (skin thickening, primarily on fingers and toes)
- **T**elangiectasias

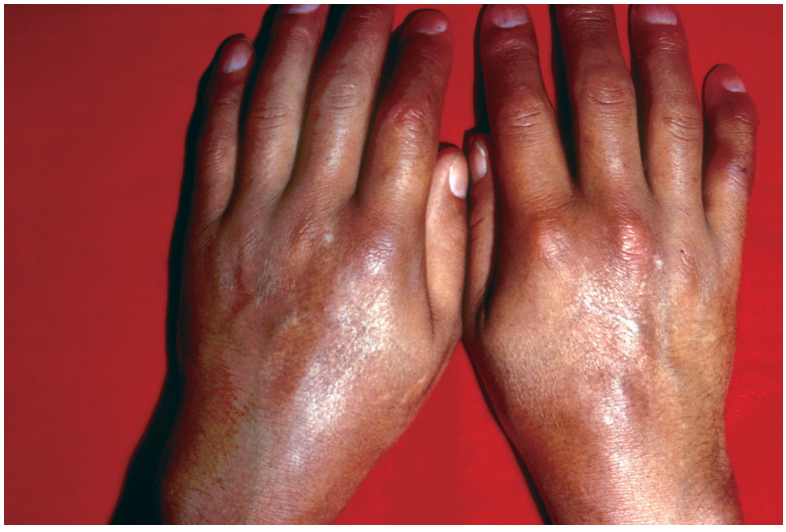


Figure 3-1. Shiny Skin of Scleroderma

Treatment. There is no cure for SSc.

- For skin manifestations, use D-penicillamine.
- For severe Raynaud phenomenon, use CCBs, specifically nifedipine.
- For hypertension, use ACE inhibitors.
- For severe systemic skin manifestations, use immunomodulating agents such as mycophenolate, rituximab, and short courses of systemic corticosteroids. Hydroxychloroquine may be used as well.

SJÖGREN SYNDROME

A 42-year-old woman presents with some peculiar symptoms lasting 1 year. She feels there is constantly something in her eyes–like dust or sand–and that dry and solid foods are painful to swallow. You are perplexed by her complaints but decide to examine her and find that she has bilateral parotid enlargement. Physical examation is otherwise normal. ANA test is positive.

Sjögren syndrome is a chronic autoimmune disease characterized by lymphocytic infiltration of the exocrine glands, resulting in xerostomia and dry eyes. It may be primary or secondary to another autoimmune disease, such as RA, primary biliary cirrhosis, or SLE.

As the syndrome progresses, it becomes a systemic disease involving major organs (lungs, kidneys, etc.), and may eventually evolve into a lymphoproliferative disease—malignant lymphoma.

Clinical Presentation.

- Itchy eyes, with a "sandy feeling" under the eyes due to reduced lacrimal production and destruction of the corneal epithelium—keratoconjunctivitis sicca
- Difficulty swallowing food
- Possible increase in dental caries
- Possible parotid enlargement
- Schirmer's test will show decreased tear production, and rose bengal stain will document corneal ulcerations
- ANAs will be positive and specifically anti-Ro (SSA) and anti-La (SSB)
- Lymphocytic infiltration of the salivary glands will be noted on biopsy

Treatment. Treatment is symptomatic only. Use artificial tears. Pilocarpine and cevimeline increase acetylcholine and increase tear and saliva production. Visceral organ involvement usually requires corticosteroids or other immunosuppressive agents.

Note

All of the diseases we just reviewed have an arthritis that is symmetric and polyarticular. RA is a disease that involves mostly the joints; the others (SLE, SSc, and Sjögren) usually have arthritis plus multiple organ involvement.

(Note that parvovirus B19 and hepatitis B may also cause symmetrical polyarthropathy.)

Clinical Recall

A 24-year-old woman is recently diagnosed with systemic lupus erythematosus. Which of the following would be appropriate counseling at the time of diagnosis?

A. The disease has no cure

B. Use sunscreen whenever outdoors to avoid flare-ups

C. You have a higher than normal chance of spontaneous abortion if you become pregnant

D. Prognosis is based on the severity and evolution of the disease

E. All of the above

Answer: E

ARTHROPATHIES

Seronegative Arthropathies, Spondyloarthropathies

A 27-year-old man presents with complaints of severe lower back stiffness and pain that have been bothering him for the past 5 years. The stiffness is most apparent in the morning when he wakes up, lasting sometimes >2 h. The only thing improving these problems is exercise. On examination there is 2/6 murmur over the second right intercostal space and decreased range-of-motion of the lumbar spine.

The spondyloarthropathies are a group of disorders that share certain clinical features and an association with the B-27 allele. Their similarities suggest that these disorders share pathogenic mechanisms.

There are 4 diseases that have similar clinical and laboratory characteristics:

Table 3-4. Seronegative Arthropathies

Disease	Characteristics
Ankylosing spondylitis **Reactive arthritis** **Psoriatic arthritis** **Enteropathic arthropathy**	• Seronegative (ANA negative, RF negative) • Involve lower back and sacroiliac joints • HLA-B27 • Extraarticular manifestations

All of the diseases have most of the 4 characteristics, plus a few others that are disease-specific.

Ankylosing Spondylitis

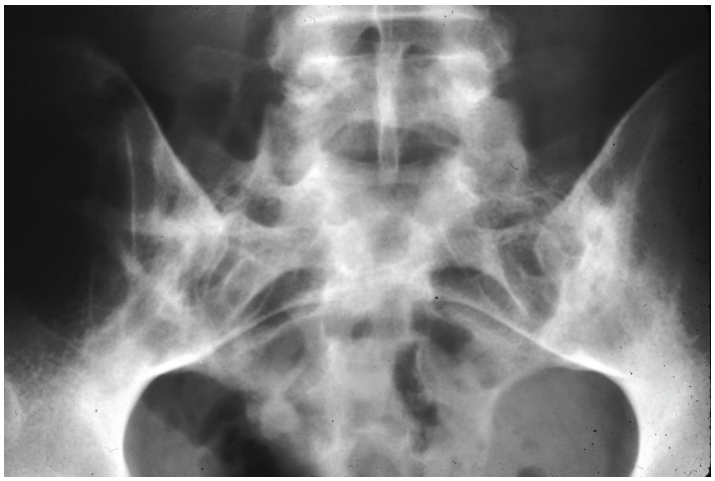
Ankylosing spondylitis (AS) is an inflammatory disorder that affects primarily the axial skeleton and peripheral joints. Etiology is unknown.

- Usually starts by decade 2 or 3 of life (very rare age >40)
- Men > women by 3–4× (this is one of the few collagen vascular diseases that affects men more than women)
- 90% of patients are positive for HLA B-27

Clinical Presentation. AS will usually present with **chronic lower back pain** in a young man (in his late twenties to early thirties). The giveaway is the **morning stiffness** lasting at least **1 h** that **improves with exercise**.

- Extraarticular manifestations (common): anterior uveitis, aortic insufficiency sometimes leading to CHF, and third-degree heart block
- Evidence of decreased spine mobility on examination: positive Schober test (measures spine flexion) and possible obliteration of the lumbar lordosis
  - Because of this, spine fracture can be seen in AS patients after minimal trauma (know that spine fractures occur with insignificant stress in older people with osteoporosis and young people with long-standing inflammatory disease of the spine, e.g., AS)
- Cervical spine is rarely, if ever, affected and only late in the disease
- X-ray shows evidence of sacroiliitis (**earliest finding**) and eventual fusing of the sacroiliac joint; chronic spine inflammation will eventually cause bamboo spine and squaring of vertebral bodies

Diagnosis is based on clinical and x-ray findings. The HLA-B27 is not commonly used as a diagnostic test.



SIU BIOMED COMM 2007—Custom Medical Stock Photo

Figure 3-2. X-ray of Pelvis in AS Demonstrating Sacroiliitis

Treatment. Treat with NSAIDs, physical therapy, and exercise. The most promising medications for AS and other spondyloarthropathies are the TNF blockers (infliximab, adalimumab, etanercept). These biologic agents are recommended for axial disease.

Unlike RA, anti-TNF medications are used first and methotrexate used later. Anti-TNF drugs work better for axial disease.

Reactive Arthritis

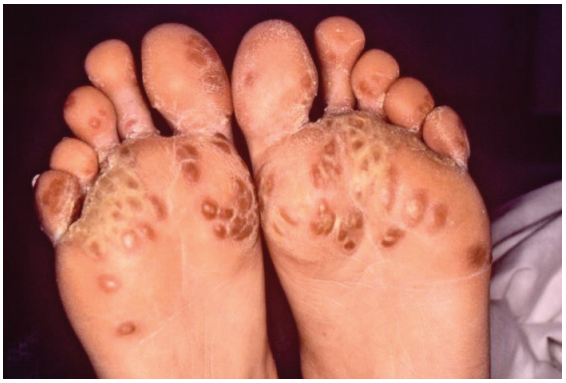
Reactive arthritis (ReA) is a seronegative arthropathy that occurs as a complication from an infection somewhere in the body. There are 2 types of infections causing different syndromes.

- One (Reiter syndrome) occurs after a nongonococcal urethritis (chlamydia, ureaplasma). These patients have distinct mucocutaneous manifestations: keratoderma blennorrhagica, circinate balanitis, oral or genital ulcers, conjunctivitis, and arthritis.
- The other ReA occurs after an infectious diarrhea caused by *Campylobacter*, *Shigella*, or *Salmonella* organisms (think of the organisms that cause enteroinvasive diarrheas; these are the same ones that cause ReA). The most common is *Campylobacter*.

Diagnosis is based on clinical criteria. X-ray findings will be consistent with a seronegative spondyloarthropathy.

Treatment. Treatment is the same as for AS. There are studies that support an accelerated recovery of Reiter syndrome caused by a chlamydial infection from prolonged tetracycline use (~3 weeks' duration). There are also studies to support the notion that prompt antibiotic use in urethritis will decrease the chance of Reiter syndrome (this is the only exception to the rule that the seronegative arthropathies are untreatable diseases).

A severe form of Reiter syndrome and reactive arthritis has been described in HIV patients. The skin manifestations are particularly aggressive in these patients and improve with antiretroviral medications.



phil.cdc.gov

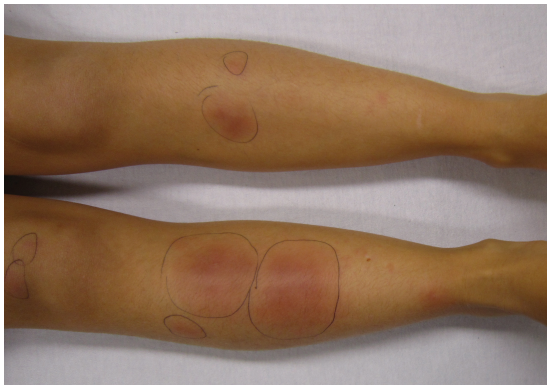
Figure 3-3. Keratoderma Blennorrhagica Seen with Reiter Syndrome

Psoriatic Arthritis

Psoriatic arthritis commonly involves the DIP joints when associated with psoriatic nail disease (pitting of the nails); this involvement may sometimes cause the characteristic sausage-shaped digit. Here, the peripheral arthritis is deforming. The psoriasis may be especially diffuse, often requiring systemic therapy.

Enteropathic Arthropathy

Enteropathic arthropathy occurs with UC and Crohn disease; sometimes the arthritis occurs with flares of the IBD. Patients may develop characteristic skin lesions: pyoderma gangrenosum and erythema nodosum. (However, neither of these skin manifestations is specific for IBD.)



Wikipedia, James Heilman, MD

Figure 3-4. Erythema Nodosum, Characteristic of Some Rheumatic Disorders

Crystal-Induced Arthropathies

The crystal-induced arthropathies—monosodium urate (MSU), calcium pyrophosphate (CPPD), calcium oxalate (CaOx), and calcium hydroxyapatite (HA)—are caused by microcrystal deposition in joints. In spite of differences in crystal morphology, they have identical clinical presentations and can be distinguished only by synovial fluid analysis.

Gout

Gout is a type of inflammatory arthritis caused by elevated uric acid in the blood. It affects mostly middle-aged men (85%), but women become increasingly susceptible to gout after menopause.

Gout most commonly presents with acute monoarthritis. As it becomes chronic, multiple joints may be involved, and deposition of urate crystals in connective tissue (tophi) and kidneys may occur.

- Metatarsophalangeal joint of the first toe is commonly affected (podagra), but other joints such as the knee, ankle, PIPs, or DIPs may be initially involved
- First episode often occurs at night, with severe joint pain waking the patient from sleep; the joint rapidly becomes warm, red, and tender (it looks exactly like cellulitis)
- Without treatment the joint pain goes away spontaneously within 3–14 days

Certain events can precipitate gout: excessive alcohol ingestion, red meat intake, trauma, surgery, infection, steroid withdrawal, drugs (diuretics such as hydrochlorothiazide and furosemide; anti-TB medications such as pyrazinamide and ethambutol), or serious medical illness.

MSU deposition causes an intense inflammatory process—red, warm joint.

Note

Gout can be very inflammatory, thus the WBCs in the synovial fluid can easily >50,000 cells at times.

Diagnosis. Serum uric acid level is of no value in the diagnosis of acute urate arthropathy. During an acute attack, serum uric acid may be normal or low, but many people with elevated serum uric acid never develop gout. Diagnosis is made by analysis of synovial fluid instead. On synovial fluid analysis, the MSU crystals are negative birefringent and needle-shaped. WBCs will range 5000–50,000. X-ray of a joint that has been involved in multiple gouty attacks will show erosive calcifications.

Treatment. With **acute gouty arthritis**, the goal is to decrease inflammation and thus prevent erosion and joint destruction; also in this stage it is very important to avoid fluctuations in serum uric acid level.

- NSAIDs
- Steroids oral (rarely intraarticular) in elderly patients who cannot tolerate NSAIDs/colchicine or in patients with renal impairment
- Colchicine is rarely to be used in acute gout but is still available

Note

- For acute gout, do not initiate allopurinol. (However, if a patient has already been taking allopurinol, do not discontinue.)
- For chronic gout, allopurinol is first-line (to prevent attacks).

With **chronic hyperuricemic gout**, the goal is to decrease uric acid levels. This is usually required for life and initiated in those whose recurrent gouty attacks cannot be corrected by low-purine diet, alcohol limitation, avoiding diuretics, etc. Unlike acute gout, the uric acid level here may help the physician to follow the effect of hypouricemic treatment.

- Allopurinol can be used in overproducers, undersecretors, or patients with renal failure or kidney stones
- Febuxostat is used in those intolerant of allopurinol
- Pegloticase dissolves uric acid: used in refractory disease

Consider the following scenario.

> A 32-year-old man comes with a history of right ankle swelling that occurred the night before. He has noticed that his ankle has been red, warm, and very painful. He occasionally drinks alcohol. On examination a red swollen ankle is noted with evidence of an effusion. Range of motion is restricted.

Note

Today, patients with gout are not assessed about being overproducers or underexcretors. Therefore, probenecid is no longer used.

The first step with this patient is **aspiration**. After confirming the diagnosis, treat with **NSAIDs**.

> Six months later, the patient returns with left knee swelling. On examination a red warm knee is noted.

The first step now is **aspiration**. After confirming the diagnosis, treat with **NSAIDs**.

> On a routine visit the same patient has had 4 documented episodes of gout, despite limiting alcohol and diet.

Now the next step is to consider **allopurinol** or **probenecid**.

> You decide to place the patient on allopurinol. He does very well for 2 years with no gouty attacks. After that he experiences another episode of right ankle swelling.

Pseudogout

CPPD crystal deposition is more common in elderly and in those with preexisting joint damage. A small percentage of the patients have metabolic abnormalities that are associated with CPPD deposition (secondary).

Remember the 4 Hs. The presence of pseudogout in a patient age <50 should raise suspicions about one of these metabolic abnormalities.

- Hyperparathyroidism
- Hemochromatosis
- Hypophosphatemia
- Hypomagnesemia

Clinical Presentation.

- Possible acute presentation like gout, or possible asymptomatic and chronic form
- Knee is most commonly affected joint; other joints commonly affected are the wrist, shoulder, and ankle

Definitive diagnosis requires the typical rectangular, rhomboid, positive birefringent crystals on synovial fluid evaluation. X-ray may reveal linear radiodense deposits in joint menisci or articular cartilage (chondrocalcinosis).

Treatment. Treat as you would treat gout. Low doses of colchicine may be considered to prevent frequent recurrences.

Clinical Pearl

Always investigate patients with pseudogout for systemic disease, especially hemochromatosis.

SEPTIC ARTHRITIS

> A 67-year-old woman with history of RA for many years presents with right shoulder pain and swelling for 2 days. She has low-grade fever. Examination reveals decreased passive and active range of motion of the right shoulder joint, as well as erythema. She asks you if this is related to an RA flare and if she should start steroids to decrease the pain.

The most common cause of infectious arthritis is gonorrhea (70% of episodes in patients age <40). Women are at greater risk during menses and pregnancy, and women are 2–3× more likely than men to develop disseminated arthritis.

In older patients, *Staphylococcus aureus* is a common cause of infectious arthritis and occurs in patients with preexisting joint destruction from other rheumatic diseases. Patients with RA have the highest risk because of chronic inflamed or destroyed joints, steroid therapy, and frequent skin breakdown over deformed joints.

Diagnosis. Acute bacterial infection may cause rapid cartilage destruction, so a patient presenting with monoarticular arthritis needs prompt diagnosis. This is done with arthrocentesis.

Further, *Staph* or *Strep* must be cleaned out of the joint space by arthrocentesis or arthroscopy.

Remember that most infected joints with gonococcal will not have positive cultures, and the Gram stain will be negative. Do *Neisseria gonorrhoeae* cultures of the throat, penis, vagina and rectum when GC is in differential.

Treatment focuses on the likely etiology. A 30-year-old woman with acute monoarticular arthritis and >50,000 WBCs in the synovial fluid without crystals should be treated with ceftriaxone. A 72-year-old man with RA with the same findings should be treated with nafcillin or vancomycin.

This disease is discussed further in the Infectious Diseases chapter.

VASCULITIS SYNDROMES

Vasculitis is an inflammatory process involving the blood vessels, resulting in a decrease of the lumen diameter and eventual ischemia of the tissues supplied. The vasculitis syndromes are stratified according to the types of vessels involved.

Granulomatosis with Polyangiitis

Granulomatosis with polyangiitis (GPA) (formerly called Wegener granulomatosis) is a small vessel vasculitis. It typically affects the respiratory tract (sinuses, nose, trachea, and lungs) and kidneys, but can involve any organ system.

Symptoms include:

- Involvement of the upper respiratory tract (**most common sign**): rhinitis, sinusitis, subglottic stenosis, and nasal ulcers (rare)
- Chronic rhinitis (common) that is unresponsive to standard treatment and that becomes increasingly worse
- Despite lack of symptoms, lungs are affected in most people; if symptoms are present, they include cough, hemoptysis, and dyspnea
- Kidney involvement (>80% of patients) (major cause of morbidity and mortality)
- Arthritis (60% of patients)
- Presence of antineutrophil cytoplasmic antibodies (C-ANCA)
  - Although a positive ANCA test is useful to support a suspected diagnosis of GPA, it is never diagnostic.
  - The C-ANCA test may be negative in some people with active Wegener. The only way to confirm the diagnosis is with a biopsy of an involved organ (usually nasal septum), demonstrating the presence of vasculitis and granulomas.

Treatment is a combination of a glucocorticoid plus an immunosuppressive agent (cyclophosphamide). This has proven by the National Institutes of Health (NIH) to be very effective for long-term survival.

Polyarteritis Nodosa

Polyarteritis nodosa (PAN) is a multisystem disease which presents with nonspecific complaints such as fever, malaise, weight loss, anorexia, and abdominal pain. The disease can affect nearly any site in the body except the lungs. It has a predisposition for organs such as the skin, kidney, nerves, and GI tract.

- Peripheral neuropathies (**very common**): tingling, numbness, and/or pain in hands, arms, feet, and legs
- Mononeuritis (e.g., foot drop)
- GI manifestations (common): abdominal pain and GI bleed (occasionally mistaken for IBD)
- Active hepatitis B infection (uncommon)
- Severe hypertension
- Testicular pain due to infarction
- Glomerulonephritis (rare)

Diagnosis.

- Biopsy of involved organs (most commonly taken from skin, symptomatic nerves, or muscle); biopsy will show pathologic changes in medium-size arteries
- Angiogram of the abdominal vessels may be helpful, since aneurysms affecting the arteries of the kidneys and/or GI tract are found

Treatment is high doses of corticosteroids and immunosuppressive drugs (cyclophosphamide).

Eosinophilic Vasculitis

Eosinophilic vasculitis (formerly called Churg-Strauss syndrome) shares many of the clinical and pathologic features of PAN; both involve the small- and medium-sized arteries. Any organ can be involved.

The cardinal manifestations are asthma, peripheral eosinophilia, and lung involvement.

The typical patient is middle-aged, with new-onset asthma. Asthma symptoms may begin long before the onset of vasculitis. Other symptoms include mononeuropathy (mononeuritis multiplex similar to PAN), transient pulmonary infiltrates on chest x-ray, paranasal sinus abnormalities, nasal polyps, and allergic rhinitis.

Diagnosis is made by biopsy. Treatment is similar to PAN (combination of prednisone and cytotoxic agent).

Note

Recently, data has emerged on the use of rituximab in lieu of cyclophosphamide. For now, cyclophosphamide is a good first-line agent.

Clinical Pearl

In patients with PAN, exclude co-existing chronic active viral hepatitis.

Note

Years ago, untreated PAN was usually fatal within weeks to months. Most deaths occurred from kidney failure, or heart or GI complications.

Note

To help remember eosinophilic vasculitis, think of it as PAN in an asthmatic patient.

Temporal Arteritis

A 72-year-old woman presents with a right-sided headache for the past 4 weeks. She has never had migraine headaches and denies blurry vision, nausea, or vomiting. The headache does not get worse at any specific time of day. She has noticed a feverish feeling and hip stiffness along with the headache.

Temporal arteritis (TA) (also known as giant cell arteritis), is a vasculitis affecting the large arteries that supply the head, eyes, and optic nerves. New-onset headache in any patient age >50 prompts consideration of this diagnosis, which if left untreated may result in permanent vision loss. Symptoms include:

- Headache and pain in one or both temples (most common symptoms)
- Scalp tenderness (pain when combing hair)
- Jaw claudication (jaw pain when chewing)
- Decreased vision or blurry vision
- Tongue numbness
- Sudden loss of vision (rare)
- Proximal stiffness (neck, arms, hips) due to polymyalgia rheumatica, a coexisting condition (seen in >25% of patients with TA) (polymyalgia rheumatic is not a myositis, so CPK will be normal)

Clinical Pearl

Always consider TA in patients with new-onset headache who are age >50–60.

Diagnosis.

- Elevated ESR (hallmark, 100% sensitive)
- Biopsy of the temporal arteries (to confirm diagnosis) will demonstrate the characteristic giant cells

Treatment. When TA is suspected and ESR is elevated, start corticosteroids immediately, before the temporal artery biopsy is performed. Do not withhold treatment.

Takayasu Arteritis

Takayasu arteritis is the other large artery vasculitis, and like temporal arteritis, involves branches off the aorta such as the renal arteries, subclavian arteries, mesenteric system and coronaries.

Patients are commonly age <50.

Clinical Presentation. Symptoms include:

- Fever, chills
- Weight loss
- Elevated ESR and CRP
- Hypertension
- GI manifestations
- Angina
- CHF in extreme cases
- Weak (even absent) peripheral pulses

Diagnosis requires angiographic imaging with MR or CT that demonstrates 3 large artery occclusions. The subclavian is usually involved.

Treatment is corticosteroids at high doses. Add a steroid-sparing agent such as mycophenalate, azathioprine, methotrexate or cyclophosphamide to help taper the steroid dose.

INFLAMMATORY MYOPATHIES

A 42-year-old woman is admitted to your service with severe proximal weakness for 2 months. Examination shows a diffuse lilac rash over the sun-exposed areas. Motor strength is 3/5 in the upper and lower proximal muscle groups.

The inflammatory myopathies are inflammatory muscle diseases that present with progressive muscle weakness. They include **polymyositis**, **dermatomyositis**, and **inclusion body myositis**.

- Patients report difficulty with tasks that involve the proximal muscles: lifting objects, combing hair, getting up from a chair.
- Fine-motor tasks that involve the distal muscles, e.g., writing, are affected only late in the disease.
- Ocular muscles are never involved (this feature **differentiates the inflammatory myopathies from myasthenia gravis and Eaton-Lambert syndrome**).

Dermatomyositis will also have skin involvement; the heliotrope rash is a purple-lilac discoloration of the face, eyelids, and sun-exposed areas of the body. Gottron's papules are the scaly lesions seen sometimes over the knuckles.

Laboratory Findings. The inflammatory destruction of muscles causes elevated muscle enzymes (sometimes up to 50-fold), CPK, and aldolase. These are the most sensitive tests to perform in patients suspected of an inflammatory myopathy.

Autoantibodies (anti-Jo-1) occur in patients with inflammatory myopathies, supporting a possible autoimmune origin.

Diagnosis. Electromyography shows evidence of myopathic potentials characterized by short-duration, low-amplitude units. Diagnosis is confirmed by muscle biopsy.

Treatment. For polymyositis and dermatomyositis, steroids are useful. Inclusion body myositis is resistant to immunosuppressive therapy.

Clinical Recall

A 55-year-old man presents with complaints of right toe pain for 8 hours. He is diagnosed with acute gouty arthritis. Which of the following is the recommended drug?

A. Allopurinol

B. Indomethacin

C. Corticosteroids

D. Methotrexate

Answer: B

Note

Autoimmune necrotizing myositis is a very rare inflammatory myositis associated with use of HMG-CoA inhibitors. Treatment is to stop the HMG-CoA inhibitor and administer an immunosuppressive agent.

Gastroenterology 4

Learning Objectives

- ❏ List diseases that should be considered for presenting complaints of epigastric pain, diarrhea, or constipation
- ❏ Describe the presentation and management of a patient with GI bleed
- ❏ Describe the epidemiology and management of diseases of the esophagus, liver, pancreas, and colon including cirrhosis, acute pancreatitis, and colon cancer
- ❏ Describe the types of malabsorption syndrome, their causes, and treatment
- ❏ Differentiate diverticular disease and different forms of IBD in terms of their presentation and treatment

DISEASES OF THE ESOPHAGUS

Most diseases of the esophagus will result in dysphagia (difficulty swallowing), yet only a few of them will result in pain on swallowing (odynophagia). Both dysphagia and odynophagia will cause weight loss if symptoms persist for more than a few days.

Dysphagia can be classified as oropharyngeal or esophageal. **Oropharyngeal dysphagia** is caused by muscular and neurologic disorders, such as stroke, Parkinson, ALS, NG, muscular dystrophy, or Zenker's diverticulum. Evaluation includes select videofluoroscopy (modified barium swallow); the patient swallows food under fluoroscopy and the upper esophageal sphincter is evaluated as the initial swallow is made. Patients with this condition present with:

- Coughing with swallowing
- Choking
- Nasal regurgitation with fluids
- Aspiration while swallowing

Patients with **esophageal dysphagia** report food "sticking" or discomfort in the retrosternal region.

Achalasia

A 32-year-old woman with no past medical history presents with "difficulty swallowing" foods for almost 1 year. She reports that food "sticks" in her chest. It is most difficult to eat solids. Her symptoms have not worsened at all over the course of the year, and her weight has been stable. Physical examination is unremarkable.

Achalasia is caused by degeneration of the myenteric plexus with loss of the normal inhibitory neural structure of the lower esophageal sphincter (LES). The LES fails to relax and there is decreased peristalsis. The LES is usually contracted to prevent the acidic gastric contents from refluxing backward into the esophagus.

The vast majority of cases are of unknown etiology. A very small number can be from Chagas disease, gastric carcinoma, or a disease that can infiltrate into the area such as lymphoma.

Note

Achalasia has no relationship with alcohol or tobacco use. This is different from esophageal cancer, which not only presents with dysphagia to solid foods and progresses to difficulty swallowing liquids, but also is more common in older patients with a long history of alcohol/tobacco use.

Clinical Presentation. Achalasia presents with progressive dysphagia to both solids and liquids simultaneously and can have regurgitation several hours after eating. The patient complains of esophageal dysphagia with possible weight loss.

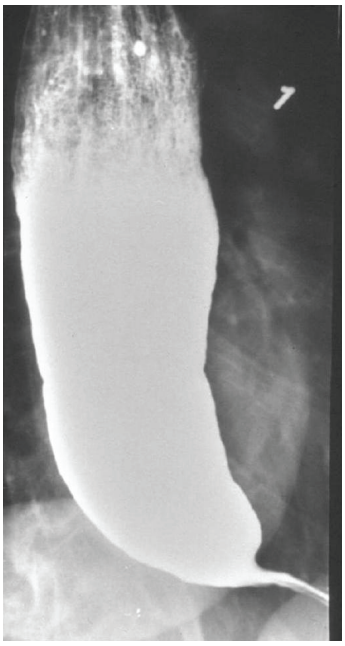
Diagnosis. Heme-positive stools, symptoms >6 months, and weight loss will confirm diagnosis. Diagnostic testing should be done in the following order:

1. Barium swallow (very accurate) will show dilation of the esophagus, which narrows into a "bird's beak" at distal end
2. Esophageal manometry (**gold standard, mandatory to confirm diagnosis**) will show increased lower esophageal (LES) resting pressure and the absence of peristalsis
3. Upper endoscopy with endoscopic U/S (to rule out adenocarcinoma [pseudoachalasia]) if there is concern for malignancy:
   - Rapid onset/progression of symptoms in <6 months
   - Rapid and significant weight loss
   - Age >50–60

Primary achalasia typically has a more insidious onset over several years and only a mild weight loss.

Treatment. The best initial treatment is pneumatic dilation or laparoscopic surgical myotomy.

- Pneumatic dilation (effective in 80–85% of patients, with 3–5% risk of perforation)
- Botulinum toxin injection into the LES (second-line) for relief of symptoms >6 months and for those who are poor surgical candidates, e.g., elderly with comorbid conditions
- CCBs and nitrates (third-line)



Wikimedia, Farnoosh Farrokhi and Michael F. Vaezi

Figure 4-1. Achalasia

Esophageal Cancer

A 62-year-old man comes for evaluation of progressive "difficulty swallowing solids and, recently, semisolids" for 4 months. He has noticed a 20-lb weight loss. His past medical history is significant for reflux esophagitis for 15 years and a 40-pack-year smoking history. On physical examination a 1.5-cm, left supraclavicular lymph node is found. The remainder of the physical examination is unremarkable.

Esophageal cancer is linked to the synergistic, carcinogenic effect of alcohol and tobacco use for cases of squamous cell cancer in the proximal two-thirds of the esophagus. Adenocarcinoma is found in the distal third of the esophagus and is associated with long-standing GERD and Barrett esophagus. The rate of development of cancer from Barrett esophagus is 0.4–0.8% per year. Squamous and adenocarcinoma are now of equal frequency.

Clinical Presentation. Esophageal cancer presents with progressive dysphagia first for solid food, then for liquids. Weight loss is prominent. Rarely, halitosis, regurgitation, and hoarseness occur. Hypercalcemia may arise, as it can with most cancers. Diagnostic testing includes:

- Barium swallow first
- Endoscopy (**mandatory**) second because this is a diagnosis which requires a tissue biopsy
- CT scan to detect the degree of local spread
- Bronchoscopy to detect asymptomatic spread into the bronchi
- Endoscopic U/S to stage

Treatment is surgical resection if the disease is sufficiently localized to the esophagus. Only 25% of patients are found to be operable. Five-year survival is 5–20%.

Chemotherapy with a 5-fluorouracil-based chemotherapy is combined with radiation to control locally metastatic disease.

Scleroderma (Progressive Systemic Sclerosis)

As many as 80–90% of patients with scleroderma will develop diminished esophageal peristalsis from the atrophy and fibrosis of the esophageal smooth muscle.

Clinical Presentation. Although there is dysphagia, the main clue to the diagnosis is simply the presence of gastroesophageal reflux symptoms in a person with a history of scleroderma. The LES will neither contract nor relax and basically assumes the role of an immobile open tube.

The most accurate diagnostic test is a motility study. Barium studies are generally unnecessary.

Treatment is a PPI e.g., omeprazole. Metoclopramide, a promotility agent, has a modest effect.

Diffuse Esophageal Spasm and Nutcracker Esophagus

> A 34-year-old man complains of "crushing" chest discomfort for 1 hour. He has no significant medical history. The ECG is normal. He is given sublingual nitroglycerin in the emergency room that improves his chest pain almost immediately.

Esophageal spastic disorders are idiopathic abnormalities of the neural processes of the esophagus. Fundamentally, diffuse esophageal spasm and nutcracker esophagus are the same disease; the only difference may be in the manometric pattern.

Clinical Presentation. Patients present with intermittent chest pain and dysphagia. The pain can simulate that of a myocardial infarction, but it bears no relationship with exertion. There is no relationship with eating, ruling out odynophagia. The pain can be precipitated by drinking cold liquids.

Barium study may show a "corkscrew"' pattern at the time of the spasm. The most accurate test for diagnosis is a manometric study, which will show high-intensity, disorganized contractions. Because the contractions are disorganized, they do not lead to the forward flow of food and peristalsis.

Treatment is a CCB, e.g., nifedipine, for dysphagia. Trazadone plus imipramine or sildenafil can relieve chest pain.

Rings and Webs

Schatzki's ring and Plummer-Vinson syndrome (PVS) reveal thin, epithelial membranes made out of squamous epithelial cells. Neither is progressive in nature, distinguishing them from achalasia.

- Schatzki's ring (**more common**) leads to intermittent dysphagia and is not associated with pain. It is more distal and located at the squamocolumnar junction proximal to the lower esophageal sphincter.
- PVS is more proximal and is located in the hypopharynx. It is typically seen in middle-aged women. PVS is associated with iron-deficiency anemia and squamous cell cancer.

Both disorders are diagnosed with a barium swallow or barium esophagogram.

Treatment is dilation procedures for both disorders. PVS may respond to treatment for the iron deficiency.

Esophagitis

Esophagitis refers to infection or inflammation of the esophagus.

- **Infection**: *Candida albicans* **(most common)**, seen with
  - HIV-positive patients with CD4 count <200/mm^3 (**most often**)
  - DM
  - Herpes simplex, cytomegalovirus, and aphthous ulcers (rarely)
- **Inflammation**

Esophagitis pain is simply from the mechanical rubbing of food against an inflamed esophagus as it passes by. It can also result from ingestion of medication and caustic substances; the direct effect of contact between the mucosa and the pill causes inflammation rather than infection.

As with most other toxin-mediated damage to an organ, diagnosis is based on the presentation and identification of the toxin in the history. The most common pills causing esophagitis are alendronate, quinine, risedronate, vitamin C, potassium chloride, doxycycline, NSAIDs, and iron sulfate. Consider pill esophagitis in a young patient who takes acne medication and who has an acute onset of odynophagia.

Symptoms include:

- Progressive odynophagia
- Painful swallowing, but food is still able to pass (until disease is extremely advanced)
- Oral thrush (70% of patients)

If there is severe pain and fever, but no thrush in a patient with CD4 count <50, think CMV esophagitis and get an endoscopy.

Treatment. If the patient is HIV-positive, assume *Candida* esophagitis and start fluconazole; improved symptoms will confirm the diagnosis. If symptoms do not improve, perform endoscopy and biopsy to exclude other causes such as HSV and CMV.

Note

The pain in esophagitis is only on swallowing, while the pain in spastic disorders is intermittent without even needing to swallow.

Clinical Correlate

Barium swallow is the incorrect test for esophagitis. It is always the correct first test for dysphagia.

Treatment for *Candida* **must be fluconazole**. Nystatin swish and swallow will not work (and is a common incorrect answer on the exam).

- 30% of patients with *Candida* esophagitis will not have oral thrush (an absence of oral candida does not rule out esophageal candida)
- Because esophagitis can also result from ingestion of medication and caustic substances, the direct effect of contact between the mucosa and the pill causes inflammation rather than infection. As with most other toxin-mediated damage to an organ, diagnosis is based on the presentation and identification of the toxin in the history. The most common pills causing esophagitis are alendronate, quinine, risedronate, vitamin C, potassium chloride, doxycycline, NSAIDs, and iron sulfate. Consider pill esophagitis in a young patient who takes acne medication and who has an acute onset of odynophagia.

Pill esophagitis is prevented by simply swallowing pills in the upright position and drinking enough water to flush them into the stomach.

Eosinophilic Esophagitis

> A young man with a history of allergies, asthma, or eczema presents with extreme solid food dysphagia. Upper endoscopy shows stacked circular rings and mucosal furrowing.

Biopsy shows marked infiltration with ≥15 eosinophils/hpf. Endoscopic findings include rings, longitudinal furrows, luminal narrowing and white exudate and plaques.

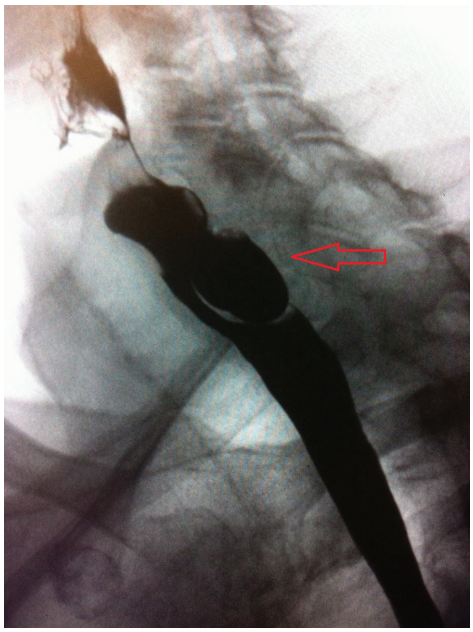
GERD can also cause esophageal eosinophilia (EE) and can mimic it, and there is commonly a crossover with both. Proximal esophageal involvement; large numbers of intraepithelial eosinophils on histologic examination; younger age; male sex; presence of dysphagia and food allergies; presence of esophageal rings, furrows, and plaques; and lack of a hiatal hernia make it more likely to be EE than GERD.

Treatment. Treat with swallowed fluticasone/budesonide or PPIs. For esophageal stricture that does not respond to medical therapy, do endoscopic dilation.

Zenker Diverticulum

> A 25-year-old medical student seeks your help because he thinks he "has bad breath." This past weekend, a most disturbing event occurred while he was watching a football game: He coughed up the chicken teriyaki he ate 2 days earlier. He claims to brush his teeth every night. The physical examination is normal. What is the next step in evaluation?

Zenker diverticulum is the outpocketing of the posterior pharyngeal constrictor muscles at the back of the pharynx.



Wikipedia, James Heilman, MD

Figure 4-2. Zenker Diverticulum

Clinical Presentation. Zenker diverticulum is a very slowly developing problem that occurs in older patients.

- Bad breath
- Difficulty initiating swallowing (due to such a proximal lesion)
- Need to repeatedly clear the throat
- Waking up with undigested, regurgitated food on the pillow (food from perhaps several days ago)

Barium study will confirm diagnosis.

Treatment. Treat with surgical resection. Endoscopy and the placement of nasogastric tubes are contraindicated because they could perforate the pharynx.

Mallory-Weiss Syndrome

Mallory-Weiss syndrome is a nontransmural tear of the lower esophagus that is related to repeated episodes of retching and vomiting.

Clinical Presentation. Although Mallory-Weiss syndrome is an esophageal disorder, the presentation is markedly different from the other problems described.

- No dysphagia or odynophagia, but rather, painless upper GI bleed
- Black stool from melena if volume of bleed >100 mL or with hematemesis if there is continued vomiting

Diagnosis is made with direct visualization on upper endoscopy.

Treatment. Typically, Mallory-Weiss tears will resolve spontaneously. It may be necessary to inject the tear with epinephrine or perform cauterization.

Clinical Recall

A 58-year-old patient presents with non-painful, progressive difficulty in swallowing solid foods for the past 6 weeks. Which of the following is the best initial test?

A. Barium swallow

B. Contrast CT of the chest

C. Endoscopy

D. Endoscopic ultrasound

E. Esophageal manometry

Answer: A

EPIGASTRIC PAIN

In most cases, there is no definite way to determine the etiology of epigastric discomfort or pain simply by examining the patient's history. Epigastric pain can be caused by the following:

- Pancreatitis (most common reason for epigastric tenderness and pain)
- Ulcer disease (associated with epigastric tenderness in <20% of patients)
- GERD
- Gastritis
- Gastric cancer (rare)

Helicobacter pylori is most strongly associated with the development of duodenal ulcers, gastric ulcers, and gastritis.

Despite these diagnostic possibilities, the most common etiology of epigastric pain is, in fact, never truly determined. This is referred to as nonulcer dyspepsia, a functional disorder in which there is persistent pain in the epigastric area but all tests are found to be normal.

Guidelines recommend upper endoscopy for patients with dyspepsia and alarm features, so the first step is to look for those. Alarm features include the following:

- Onset age >60
- Anemia
- Dysphagia
- Odynophagia
- Vomiting
- Weight loss
- Family history of upper GI malignancy
- Abdominal mass or lymphadenopathy on examination

Any alarm feature requires upper endoscopy. Endoscopy is also indicated if symptoms have not resolved with antisecretory therapy, such as PPIs.

If there are no alarm features in a patient age <60, use a noninvasive test-and-treat approach for *H. pylori,* such as a urea breath test or stool antigen test.

Treatment. Although endoscopy is the most accurate way to diagnose an ulcer, one can empirically treat ulcers, reflux disease, and gastritis.

- Start by testing for *H. pylori*. If positive, treat. If negative, give a PPI.

Gastroesophageal Reflux Disease

> A 32-year-old man comes to the ED for substernal chest pain of 2 hours' duration. He says that he sometimes gets this pain while lying in bed at night. He is otherwise free of symptoms, except for a nonproductive cough that he has had for the past month. Physical examination is unremarkable. ECG is normal. He is given sublingual nitroglycerin and notes that his chest discomfort is worsened.

Gastroesophageal reflux disease (GERD) is caused by the abnormal flow of the acid gastric contents backward from the stomach up into the esophagus (the lower esophageal sphincter).

A number of factors can cause decreased tone or loosening of the sphincter.

- Nicotine, alcohol, caffeine
- Peppermint, chocolate
- Anticholinergics
- CCBs
- Nitrates

When the tone of the lower esophageal sphincter decreases, acid is more likely to reflux backward into the esophagus, particularly when the patient is lying flat. GERD can still occur in the absence of these precipitating factors and can often simply be idiopathic in origin.

Clinical Presentation. GERD will present with heartburn (burning substernal pain); sore throat; a metal-like taste in the mouth; hoarseness; cough and wheezing. In addition, it is often associated with pain in the substernal area. Symptoms are worse after a meal or while lying flat.

The most accurate diagnostic test is a 24-hour pH monitor; an electrode is placed several centimeters above the gastroesophageal junction, and a determination is made of what the average pH is in that area. Normal endoscopy does not exclude reflux disease.

Note the following order when working up GERD:

- Initiate PPI; if no improvement after 4–8 weeks, increase PPI to 2×/day (before EGD) for 4–8 weeks and make sure patient is taking properly (30–60 min before meals)
- If no improvement, do EGD: If EGD shows esophagitis, that confirms GERD and 24-hour pH monitoring is not needed. If EGD is normal, do ambulatory 24-hour pH monitoring (while off the PPI) and if results are consistent with GERD, do Nissen fundoplication.

Note

Any alarm features such as bleeding, weight loss, or difficulty swallowing requires upper endoscopy.

Note

There is no point in treating *H. pylori* without evidence of disease such as gastritis or ulcer disease.

Note

The lower esophageal sphincter is not a true anatomic sphincter (it cannot be found in a cadaver); it is created by the different responses of the smooth muscle cells in the distal esophagus.

In clear cases of epigastric pain going under the sternum and associated with a respiratory complaint or bad taste in the mouth, **initiate therapy immediately** with antisecretory medications such as PPIs.

Treatment starts with lifestyle modification: avoid nicotine/alcohol/caffeine/chocolate/late-night meals and elevate the head of the bed 6–8 inches with blocks to keep acid in the stomach.

Next, give a PPI to increase the pH of the gastric contents to >4.0.

- Omeprazole, esomeprazole, lansoprazole, pantoprazole, or rabeprazole (**all equally effective**)
- Side effects of PPIs include:
  - Increased risk of *C. difficile* infection
  - Aspiration pneumonia
  - Osteoporosis
  - Microscopic colitis
  - Hypomagnesia
  - Vitamin B12 deficiency
  - Interstitial nephritis
  - Hip fracture
- If no response to PPIs (<5% of patients) or there are refractory side effects (headaches, diarrhea): surgery to tighten the sphincter (traditionally, a Nissen fundoplication is done laparoscopically) (do a motility study beforehand to avoid iatrogenic dysphagia)
- H2 blockers only for very mild, intermittent symptoms (less effective than PPIs)

Note

For the exam, make sure you know the side effects of PPIs.

Note

In patients with chronic cough (≥8 weeks), symptoms typical of GERD (heartburn, cough that is worse after a large meal), and negative chest x-ray, initiate a PPI as the next most appropriate step.

Barrett Esophagus

Barrett esophagus is a complication of long-standing reflux disease. After several years of GERD, the epithelium of the lower esophagus undergoes histologic change from a normal squamous epithelium to a columnar epithelium.

Men age ≥50 with chronic GERD (5+ years) and additional risk factors (nocturnal symptoms, hiatal hernia, obese, smokers) should be screened.

Patients with Barrett esophagus should have repeat endoscopy every 3–5 years to see whether dysplasia or esophageal cancer has developed:

- If low-grade dysplasia, treat endoscopically or repeat endoscopy in 6–12 months
- If high-grade dysplasia, do radiofrequency ablation, photodynamic therapy, or endoscopic mucosal resection
- The usual rate of progression to cancer is about 0.5% per year.

Do not check barium swallow, as it will be normal.

Treatment. PPIs for all patients

Peptic Ulcer Disease

(PUD) includes both duodenal and gastric ulcers. The most common causes of ulcer disease are *H. pylori* (80–90% of duodenal ulcers and 70–80% of gastric ulcers) and NSAIDs.

About 10–20% of ulcers are idiopathic, with no clear etiology.

- NSAIDs can cause ulcer formation because they decrease the normal production of the mucous barrier protecting the epithelial cells of the gastric mucosa. Prostaglandins, the major stimulant for mucous production that forms this protective barrier, are inhibited by NSAIDs and hence diminish the protective barrier of the stomach lining. Screen all patients with PUD for *H. pylori*, regardless of NSAID use.
- Steroid use by itself does not cause PUD and is therefore not a routine indication for stress ulcer prophylaxis.
- Smoking and alcohol use do not cause PUD, but they can delay healing and are associated with the development of gastritis.

Parietal cells in the stomach produce acid. The 3 stimulants to the production of acid from the parietal cells are gastrin, acetylcholine, and histamine.

- Gastrin is produced by G cells in the stomach, and its release is stimulated by distention of the stomach, the presence of amino acids, and vagal stimulation. Vagal stimulation also releases acetylcholine and gastrin-releasing peptide. However, the single most important stimulant to gastrin release is distention of the stomach.
- Histamine is released by enterochromaffin-like cells present in the same glandular elements of the stomach that have the parietal and chief cells. Chief cells release pepsinogen, which is converted to pepsin by the acid environment of the gastric lumen. Histamine directly stimulates the parietal cells to both release acid and potentiate the effects of acetylcholine and gastrin on the parietal cells. This is why H2 blockers such as cimetidine, famotidine, and ranitidine inhibit acid release.

Zollinger-Ellison syndrome is the excessive production and release of gastrin from the pancreas. Somatostatin is the counterbalance to this system, inhibiting the release of gastrin and histamine, as well as having a direct inhibitory effect on the production of acid from the parietal cells. Secretin is released from the S cells of the duodenal lining. The main stimulant to the release of secretin is the presence of acid in the duodenum. Secretin inhibits the production of gastrin, as well as stimulates pancreatic and biliary bicarbonate production and release.

Clinical Presentation. The most common presentation of ulcer disease is midepigastric pain. There is no definite way to distinguish between duodenal and gastric ulcer simply by symptoms. Gastric ulcer is often associated with pain on eating (frequently leading to weight loss), while duodenal ulcer is thought to be relieved by eating. However, these associations are only rough approximations, and endoscopy is still required for a definite diagnosis.

Tenderness of the abdomen is unusual with ulcer disease. More than 80% of cases are not associated with abdominal tenderness in the absence of a perforation. Nausea and vomiting are occasionally found with both of them.

Note

For burn victims >30% BSA and intubated patients, the correct answer is stress ulcer prophylaxis is.

Diagnosis. Ulcer disease is best diagnosed with upper endoscopy. Barium studies are inferior.

- If patient age <60 and has no alarm symptoms, use non-invasive testing and treat for *H. pylori*. If *H. pylori* is negative, give trial of PPIs. If symptoms persist, perform endoscopy.
- If patient age >60 or has alarm symptoms (weight loss, anemia, heme-positive stools, or dysphagia), perform endoscopy.

Note

H. pylori can be associated with ITP.

Diagnosis of *H. pylori* is based on urea breath testing, stool antigen testing, or biopsy with histology or rapid urease testing. The first 2 tests are non-invasive.

- Before testing for *H. pylori*, patient must be off PPIs for 2 weeks and antibiotics for 4–8 weeks (can cause false-negatives).
- Biopsy with histology can be done on treatment.
- Biopsy with rapid urease testing can be false-negative on treatment. Bleeding ulcers can cause a false-negative biopsy result, so if there is a bleeding ulcer on the endoscopy, send another test for *H. pylori*, like urea breath test or stool antigen.

Note

Gastric ulcers must be biopsied to exclude cancer.

Do not check serum antibodies as they will not indicate whether this is a past or present infection.

Treatment centers around treatment for *H. pylori*.

- PPI plus antibiotics (effective in >90% of patients) for 10–14 days (the PPI may be continued to heal the gastric mucosa)
  - The PPIs omeprazole, lansoprazole, pantoprazole, rabeprazole, and esomeprazole are all equal in efficacy
  - *H. pylori* resistance to clarithromycin has increased in recent years
    - If local resistance rates >15%, previous treatment with a macrolide, or eradication rates with clarithromycin-based triple therapy <85%, use metronidazole, tetracycline, bismuth, or a PPI; another alternative is a PPI + levofloxacin + amoxicillin
    - If triple therapy fails, use another regimen
- Repeat endoscopy for gastric ulcer is needed only if symptoms persist or if biopsy was not done the first time. Follow-up endoscopy for duodenal ulcer is not needed.

Wait 4–8 weeks post-treatment to check for eradication with urea breath test or fecal antigen test. This should be done in all cases after treatment because of risk of PUD and gastric malignancy.

- If **organism was not eradicated**: repeat treatment with different antibiotics, plus bismuth subsalicylate. Explore sensitivity testing for the organism.
- If **organism was eradicated** but ulcer persists/worsens: consider Zollinger-Ellison syndrome.

Ordinary ulcer not related to *Helicobacter* can be treated with PPIs alone. Stop NSAIDs. If unable to stop aspirin or NSAIDs, give COX-2 inhibitor + PPI. Sucralfate does not help and should not be used.

Give PPI for prophylaxis if patient is high risk. Risk factors include:

- History of PUD or GI bleed
- Age 65 years or older
- Chronic comorbid illness
- High-dose NSAID use
- Concomitant use of aspirin (of any dose), anticoagulants, other NSAIDs, or glucocorticoids

Indications for surgery in PUD:

- UGI bleed not amenable to endoscopic procedures
- Perforation
- Refractory ulcers
- Gastric outlet obstruction (can change endoscopic dilation)

Gastritis

Gastritis is inflammation, erosion, or damage of the gastric lining that has not developed into an ulcer.

- **Type B** gastritis (most common) caused by:
  - Alcohol, NSAIDs, *Helicobacter*, head trauma, burns, and mechanical ventilation
  - **Increased gastric acid production**
- **Type A** gastritis caused by:
  - Atrophy of the gastric mucosa
  - Associations include vitamin B12 deficiency (autoimmune), **diminished gastric acid production** and achlorhydria (patients with achlorhydria will have markedly elevated gastrin because acid inhibits gastrin release from G cells)
  - MALT leads to metaplasia (and possible dysplasia) and then to gastric cancer

Clinical Presentation. Patients typically present with asymptomatic bleeding (as hematemesis or melena). Nausea and vomiting may occur.

When the gastritis is severe and erosive, abdominal pain will occur in the same area that patients with ulcer disease feel theirs.

Diagnosis and Treatment.

- Diagnosis and treatment of *Helicobacter* are the same as that for gastritis (described for ulcer disease).
- Diagnosis of vitamin B12 deficiency and pernicious anemia are made initially with low B12 and increased methylmalonic acid.
- Pernicious anemia is confirmed with the presence of antiparietal cell antibodies and anti-intrinsic factor antibodies; treatment is B12 replacement, as with all cases of B12 deficiency.
- Evaluate all patients who have pernicious anemia for gastric adenocarcinoma with upper endoscopy and biopsy.

Zollinger-Ellison Syndrome

A 42-year-old woman presents with complaints of diarrhea for 6 months. She has stopped all dairy products but there has been no improvement. There is no blood or pus with the stools. She takes maximum doses of omeprazole daily, along with famotidine, and still has ulcer symptoms. She has a mild hypercalcemia.

Zollinger-Ellison syndrome (ZES) is hypergastrinemia caused by cancer of the gastrin-producing cells. There is no known cause.

- 50% are located in the duodenum
- 25% are located in the pancreas
- <20% are associated with MEN type 1, or a parathyroid/pituitary/pancreatic tumor

Note

The presence of hypercalcemia is the clue to detecting MEN-1. This is because of the hyperparathyroidism.

More than 95% of patients with ZES present with ulcer disease. Of those, <1% have an underlying ZES or gastrinoma. Symptoms include:

- Ulcers that are recurrent after therapy, multiple in number, occur in the distal portion of the duodenum, or are resistant to routine therapy
- Diarrhea (70% of patients), i.e., ordinary watery diarrhea or steatorrhea (due to inactivated lipase from large volume of acid passed into the duodenum)
- Metastatic disease (evident in 30% of patients, with an additional 20% developing it later)

Note

All patients on an H2 blocker or PPI will have elevated gastrin. (The main stimulus to the suppression of gastrin release is acid, so if acid production is suppressed, then gastrin goes up.) So to diagnose ZES, the patient must have stopped the medication several days prior.

Diagnosis. An elevated gastrin level is indicative of ZES, but testing must occur after the patient has been off antisecretory therapy for several days.

Diagnosis is the combination of elevated gastrin and increased gastric acidity (must check gastric pH to make diagnosis; if pH >4, it is not a gastrinoma). The secretin stimulation test is positive (abnormal) if there is a rise in gastrin level after the injection of secretin (normally, secretin should suppress gastrin release).

Other causes of increased gastrin include:

- Pernicious anemia
- Chronic gastritis
- Renal failure
- Hyperthyroidism

After confirming a diagnosis of gastrinoma, the most important step is to determine if the lesion is localized or metastatic.

- Localized lesions can be surgically removed.
- Metastatic disease can be suppressed only with PPIs
  - U/S, CT, and MRI (60–80% sensitive to detect metastatic disease)—specific enough to prove the presence of tumor if positive but not sensitive enough to safely exclude disease if negative
  - Endoscopic U/S (**most sensitive test**)
  - Nuclear test, somatostatin-receptor scintigraphy (90% sensitive to detect metastatic disease)

Treatment. Localized disease is surgically resected and metastatic disease is treated with the long-term administration of PPIs simply to block acid production.

Gastroparesis

Gastroparesis, or delayed gastric emptying, results in delayed movement of food from the stomach to the small intestine. The most common association is diabetes. Electrolyte problems with potassium, magnesium, and calcium can also weaken the musculature of the bowel wall.

Clinical Presentation. Patients with gastroparesis present with early satiety, postprandial nausea, and a general sense of increased abdominal fullness due to decreased motility of the stomach and the accumulation of food there. Gastroparesis generally occurs in those presenting with abdominal pain and bloating and those with a long-standing history of diabetes, a long-standing history of poor glycemic control, retinopathy, neuropathy, and nephropathy. It can accompany scleroderma, hypothyroidism, anti-cholinergic use, and narcotic use.

Diagnosis. The first test should be endoscopy. Then, do the gastric-emptying study, where radioisotope-labeled food is ingested to measure transit time through the stomach. In a long-term diabetic, a diagnosis of diabetic gastroparesis is generally obvious as the cause of bloating, vomiting, and nausea, after endoscopy excludes other diseases. **Make sure blood glucose <275 mg/dL before testing** because severe hyperglycemia can impair gastric emptying.

Treatment. Treatment is agents that will increase motility of the stomach, such as erythromycin or metoclopramide. Also, smaller, more frequent portions of food are recommended, since emptying from the stomach is faster when there is less food.

Metoclopramide can cause tardive dyskinesia, Parkinsonism, and dystonia. If patients develop extrapyramidal symptoms, use promethazine.

Dumping Syndrome

Dumping syndrome is an increasingly rare disorder because surgery is so infrequently needed anymore for ulcer disease. It was far more common in the past, when vagotomy and gastric resection were performed to treat severe ulcer disease.

Dumping syndrome is caused by 2 phenomena.

- First, there is the rapid release of hypertonic chyme into the duodenum, which acts as an osmotic draw into the duodenum, causing intravascular volume depletion.
- Next, there is a sudden peak in glucose levels in the blood because of the rapid release of food into the small intestine. This is followed by the rapid release of insulin in response to this high glucose level, which then causes hypoglycemia to develop.

Patients present with sweating, shaking, palpitations, and lightheadedness shortly after a meal.

Treatment. Treatment is supportive. Eat multiple, small meals.

Nonulcer Dyspepsia

When all the causes of epigastric pain have been excluded and there is still pain, fullness, or burning sensation, the diagnosis is nonulcer (or functional) dyspepsia. The cause of nonulcer dyspepsia is unknown.

Treatment is symptomatic, with antacids, H2 blockers, PPIs,

- If there are no alarm symptoms, test and treat *H. pylori*. If negative, treat with PPI.
- If there are alarm symptoms or refractory symptoms, do endoscopy.
- Try a low-dose tricyclic antidepressant if symptoms do not respond to PPI or H2-blocker therapy.

Clinical Recall

A 36-year-old man complains of intermittent, worsening epigastric pain radiating to the back for the past 3 months. He claims to drink alcohol only during business trips but admits to blacking out several times from too much alcohol. Which of the following is the most likely cause of his symptoms?

A. Barrett's esophagus

B. Candida esophagitis

C. Gastritis

D. GERD

E. Pancreatitis

Answer: E

INFLAMMATORY BOWEL DISEASE

Inflammatory bowel disease (IBD) describes 2 disease entities: **Crohn disease** (CD) and **ulcerative colitis** (UC). They can be discussed simultaneously because of the large degree of overlap in terms of presentation, testing, and treatment.

- Idiopathic disorders of the bowel associated with diarrhea, bleeding, weight loss, fever, and abdominal pain
- Most accurately diagnosed with endoscopy and sometimes barium study, "string sign" on small bowel follow through after barium meal in CD
- Treat with anti-inflammatory medications such as mesalamine, azathioprine, and 6-mercaptopurine (6MP); steroids are reserved for acute exacerbations

Clinical Presentation. IBD presents with fever, diarrhea, weight loss, and, occasionally, abdominal pain and bleeding. The extraintestinal manifestations of IBD are episcleritis, scleritis and iritis, sclerosing cholangitis, joint pains, and skin manifestations such as pyoderma gangrenosum or erythema nodosum.

Table 4-1. CD versus UC

Crohn Disease	Ulcerative Colitis
Linear, stellate deep ulcerations with **skip lesions** involving entire GI tract	Mucosal edema, erythema, friability, ulceration
Granulomas, transmural involvement	Bloody diarrhea common; diarrhea prominent, tenesmus, urgency, hematochezia
Abdominal pain prominent; inflammatory masses	**Altered crypt architecture with shortened branched crypts and crypt abscesses**
Smoking is risk factor	Smoking alleviates
Rectal sparing	Rectum always involved
Cobblestone appearance	Limited to large bowel
Strictures and fistulas	No skip lesions, anal involvement, or fistulas
Complications include diarrhea, calcium oxalate kidney stones, and cholesterol gallstones	

Note

Sclerosing cholangitis does not correlate to disease activity.

Diagnosis. IBD is diagnosed with endoscopy and sometimes barium study. (CD can cause deficiency of B12, K, calcium, and iron because of malabsorption.)

- **Anti–*Saccharomyces cerevisiae* antibodies (ASCA) are associated with CD**, while **antineutrophil cytoplasmic antibody (ANCA) is associated with UC**.
- If a patient is **ASCA-positive and ANCA-negative, he has a >90% chance of having CD**.
- If a patient is **ASCA-negative and ANCA-positive, he has a >90% chance of having UC**.
- With CD, prothrombin time may be prolonged because of vitamin K malabsorption. Also, kidney stones are more often seen because the fat malabsorption causes reduced calcium and increased absorption of oxalate. Use cholestyramine to treat calcium oxalate stones.

Note

Always check stool studies, especially *C. difficile* toxin during a flare.

Treatment. Therapy is divided into active and maintenance.

Note

- Check thiopurine methyltransferase level before starting azathioprine and 6-mercaptopurine, as they are contraindicated in 1 in 300 patients who lack this enzyme and are at high risk for drug toxicity.
- Do not give allopurinol or febuxostat with these drugs (they are also metabolized by xanthine oxidase).

Clinical Correlate

Patients with UC are hypercoagulable.

Note

For Crohn disease, 5-ASAs have recently been proven to have little efficacy. **TNF-alpha inhibitors are now the most common treatment for Crohn**.

Note

Check PPD, HBV, HCV prior to initiating anti-TNF agent.

Table 4-2. Treatment of CD versus UC

Crohn Disease	Ulcerative Colitis
5-ASAs are often ineffective	Depends on severity of disease
Mild: For active disease prednisone or budesonide For maintenance azathioprine and 6-mercaptopurine	**Mild**: 4 bowel movements/day, mild bleeding, normal labs Mesalamine or sulfasalazine (causes reversible infertility in men and leukopenia by its sulfapyridine group)
Moderate: fever, weight loss, anemia, abdominal pain, nausea/vomiting For active steroids For maintenance azathioprine and 6-mercaptopurine or methotrexate For remission anti-TNF antibodies	**Moderate**: 4–6 bowel movements/day For active disease prednisone For remission budesonide For long-term maintenance azathioprine and 6-mercaptopurine (associated with drug-induced pancreatitis) to try to keep patients off steroids
Severe to fulminant: high fever, vomiting, rebound, obstruction For acute exacerbations, IV steroids or anti-TNF (**better choice**), possible surgery	**Severe**: >6 bowel movements/day, bleeding, fever, tachycardia, ESR >30 mm/h, anemia For acute exacerbations that fail steroids and for maintenance if azathioprine and 6-mercaptopurine fail or are contraindicated, IV steroids followed by anti-TNF-alfa (infliximab, adalimumab, golimumab)
Fistula: anti-TNF For induction and maintenance anti-TNF antibodies (infliximab, adalimumab, certolizumab); if anti-TNF fails, use natalizumab (a monoclonal antibody to integrin-alfa-4 on leukocytes) (can cause PML so check JC virus antibodies first)	
For those with perianal disease ciprofloxacin and metronidazole For those who form fistulae or have disease refractory to other therapies infliximab	
Surgery is not very effective; disease tends to reoccur at the site of anastomosis	Surgery is curative; almost 60% of patients will require surgery within 5 years after diagnosis due to refractory symptoms or severe disease

For both, start screening colonoscopy 8–10 years after diagnosis and repeat every 1–2 years.

DIARRHEA

Diarrhea is increased frequency or volume of stool per day (alternatively, it can be defined as few stools per day but with watery consistency). The most common causes include an infectious, antibiotic-associated, or lactose-intolerance etiology, irritable bowel syndrome, and carcinoid syndrome.

The patient is often hypotensive, febrile, and experiencing abdominal pain.

Diagnosis. The first step in the evaluation of diarrhea is to see if there is hypovolemia as defined as hypotension or orthostasis. This is more important than determining specific etiology because the patient could die while waiting for the results to come back.

Treatment. No matter the etiology, if the patient is hypotensive, febrile, and having abdominal pain, admit as inpatient and give IV fluids and antibiotics. Blood in the stool is especially serious and is probably the single strongest indication for the use of antibiotics, such as ciprofloxacin.

Infectious Diarrhea

The majority of acute diarrhea is viral and self-limited. *Clostridium difficile* toxin and stool *Giardia*-antigen testing are done when there are clues to these diagnoses in the history.

With bacterial diarrhea, the most common causes are *Campylobacter* and *Salmonella*, especially in patients with sickle cell and achlorhydria. A definitive determination of the etiology can only be made with a stool culture.

Note

With management of diarrhea, determine **when to admit** the patient and **when to use IV fluids and antibiotics**. That is more important than determining the precise causative agent.

Table 4-3. Clues to the Diagnosis of Infectious Diarrhea Prior to Results of Culture

Causative Agent	Patient Symptoms or History	Additional Comments
Bacillus cereus	• Ingestion of refried Chinese food and the spores from *Bacillus* that it contains • Vomiting is prominent • Blood is never present	Short incubation period (1–6 hours)
Campylobacter	Reactive arthritis, Guillain-Barré syndrome	Most common cause of bacterial gastroenteritis
Cryptosporidia, Isospora	Found in HIV-positive patients with <100/mm^3 CD4 cells	—
E. coli 0157:H7	Ingestion of contaminated hamburger meat; the organism can release a Shiga toxin, provoking hemolytic uremic syndrome	Hemolytic uremic syndrome happens when organism dies; that is why antibiotics are contraindicated. Platelet transfusion is also contraindicated, even if platelet count is low because new platelets may only make it worse.
Giardia	• Ingestion of unfiltered water, as on a camping trip in mountains or lake • Blood is never present • Abdominal fullness, bloating, and gas	If not eradicated, can simulate celiac disease in terms of causing fat and vitamin malabsorption
Salmonella	Ingestion of chicken and eggs, dairy products	—
Scombroid	Ingestion of contaminated fish; almost immediate vomiting, diarrhea, flushing, and wheezing	Organisms invade, producing and then releasing histamine into the flesh of fish, such as tuna, mahi mahi, and mackerel
Shigella, Yersinia	No clues strong enough to point to etiology until the results of stool culture are known	*Yersinia* can mimic appendicitis. Also common in people with iron overload, e.g., hemochromatosis.
Vibrio parahaemolyticus	Ingestion of raw shellfish, such as mussels clams	Typically presents as severe systemic gastroenteritis in patients with underlying disease (esp. chronic liver disease)
Vibrio vulnificus	• Ingestion of raw shellfish (particularly affects those with underlying liver disease) • Skin bullae	Typically presents as severe systemic gastroenteritis in patients with underlying disease (esp. chronic liver disease or disorders of iron metabolism)
Viral	Children in day-care centers; absence of blood and white cells	No systemic manifestation
Staphylococcus aureus	• Ingestion of dairy products, eggs, salads • Upper GI symptoms (nausea/vomiting) predominate; rarely diarrhea	Short incubation period (1–6 hours)
Ciguatera-toxin	Ingestion of large reef fish (grouper, red snapper, barracuda); 2–6 hours after ingestion, neurological symptoms leading to paresthesia, weakness, reversal of hot/cold	—

Diagnosis. Only send stool studies if condition does not resolve in 1 week. Invasive organisms need 24–36 hours to produce their effect and never produce blood in the stool within the first few hours of ingestion (except the protozoan *Entamoeba histolytica*, which can give blood or white cells in stool). The most definitive test for these bacterial organisms is stool culture.

The invasive organisms are:

- *Salmonella*
- *Shigella*
- *Campylobacter*
- *Vibrio parahaemolyticus*
- *Yersinia*
- *E. coli*
- *Vibrio vulnificus* (think fishermen exposed to sea water or eating raw oysters)

Cryptosporidiosis diagnosis requires a unique test—a modified acid-fast test; it cannot be detected reliably by the routine ova and parasite exam.

Giardia diagnosis is best made with an ELISA stool antigen test (a single test has 90% sensitivity, whereas 3 stool ova and parasite exams have only 80% sensitivity). Consider this for chronic diarrhea in patients exposed to young children or who drank water from a lake or stream.

Treatment. Most cases of food poisoning and infectious diarrhea will resolve spontaneously and will not need antimicrobial therapy. Even when they cause severe disease, as defined by high-volume stools with dehydration, antibiotics generally do not help. Use antibiotics if there is abdominal pain, blood in the stool, and fever >7 days.

The decision to use antibiotics is always made prior to knowing the result of the stool culture, so the treatment is always empiric and then modified when the culture results are known. The best empiric therapy for infectious diarrhea is ciprofloxacin or the other fluoroquinolones ± metronidazole. Macrolides are preferred for *Campylobacter* when indicated because of increasing resistance to fluoroquinolones.

Do not give antibiotics for *E. coli* 0157:H7, as that precipitate HUS.

Scombroid poisoning is treated with antihistamines, such as diphenhydramine. *Giardia* is still treated primarily with metronidazole. A newer agent for *Giardia* is tinidazole, which is effective in a single dose. Cryptosporidiosis is treated with nitazoxanide, although it has limited efficacy. The truly effective therapy for cryptosporidiosis is to raise the CD4 count to >100/mm^3 with antiretrovirals. Nitazoxanide is superior to paromomycin for cryptosporidium.

There is no specific therapy for viral diarrhea. Patients are managed with fluid and electrolyte support until the infection resolves.

For chronic diarrhea (>4 weeks), think of the following:

- Use of artificial sweeteners (get diet history)
- Giardia if camping or exposed to children (daycare worker)
- If bloating and discomfort are relieved by bowel movement with no weight loss: **IBS, test for celiac**

Note

- TMP/SMX for *Isospora*
- Doxycycline for *Vibrio vulnificus*
- Rifaximin for travelers' diarrhea

Note

Prophylactic antibiotics for traveler's diarrhea is never a correct approach.

- If woman age 45–60, unrelated to food (nocturnal diarrhea), no abdominal pain or weight loss, and normal colonoscopy, think microscopic colitis; biopsy must be done to diagnose (will see collagenous or lymphocytic colitis); associated with NSAIDs, SSRIs, and PPIs; treat with loperamide, bismuth, or budesonide for severe cases (stop NSAIDs, SSRIs, PPIs)
- Small intestinal bacterial overgrowth: nocturnal diarrhea due to overgrowth of bacteria in the small bowel; think of this in patient with poorly controlled diabetes, scleroderma, or history of gastric bypass surgery; there will be B12 deficiency with elevated folate (bacteria produce folate): check glucose hydrogen breath test or empiric antibiotics (usually rifaximin)
- Flushing and wheezing: carcinoid syndrome; check urine 5-HIAA

Antibiotic- and *C. difficile*-Associated Diarrhea

Antibiotic-associated diarrhea (AAD) is a benign, self-limited diarrhea following the use of antimicrobials. Typically, no pathogens are identified; the diarrhea is caused by changes in the composition and function of the intestinal flora, as well as increased motility (common with agents like erythromycin). Most patients respond to supportive measures and discontinuation of antibiotics.

***Clostridium difficile-associated* diarrhea** (*C. diff*) refers to a spectrum of diarrheal illnesses caused by the toxins produced by *C. diff*, including severe colitis with or without the presence of pseudomembranes. (For exam purposes, this discussion will focus on *C. diff*.)

Pathogenesis. Any antibiotic can lead to diarrhea with *C. diff*, although antibiotics that are broad spectrum are more likely to do so. Clindamycin may have one of the highest frequencies of association, as do fluoroquinolones and cephalosporins.

C. diff diarrhea is largely a nosocomial disease and is the most frequent cause of diarrhea in hospitalized patients. It occurs infrequently in the outpatient setting, other than in patients confined to nursing homes. Research suggests a significant association between *C. difficile* and the use of PPIs.

Clinical Presentation and Diagnosis. The clinical manifestations of *C. diff* may vary from mild diarrhea to fulminant colitis. If a patient develops diarrhea several days to weeks (even up to 8 weeks) after using antibiotics, evaluate for *C. diff*. Marked leukocytosis and systemic symptoms are evident in severe cases.

- Until a few years ago, the diagnostic method of choice for *C. difficile* colitis was the enzyme-linked immunosorbent assay (ELISA), based on toxin detection in the stool. While ELISA is fast, inexpensive, and has excellent specificity, its sensitivity is variable (75–85%).
- The newer preferred method of diagnosis is the nucleic acid amplification (LAMP, loop-mediated isothermal amplification) assay, which may include the real-time polymerase chain reaction (PCR) or loop-mediated isothermal amplification test (both of which detect the toxin A and B genes responsible for the production of toxins). LAMP has specificity 94–100% and sensitivity 90–100%. There is no benefit to testing multiple stool specimens or repeat testing following a positive test.

Treatment.

- **Severe *C. diff*** (WBC >15,000 or increased serum creatinine >1.5 × normal): oral vancomycin, not fidaxomicin
- **Initial infections**: oral vancomycin or fidaxomicin
- **Fulminant infections** (ileus, hypotension, shock, toxic megacolon): oral vancomycin + IV metronidazole. (IV vancomycin will have no effect in the bowel because it does not pass bowel wall. Similarly, oral vancomycin will have no systemic effect.)

If there is a second recurrence, use a tapered and pulsed course of oral vancomycin (6–8 weeks). It must be 6 weeks to be effective and it must be tapered.

- If vancomycin was used for the initial episode, try fidaxomicin, which seems to reduce the number of episodes of recurrent *C. difficile* colitis.
- Alternatively, consider fecal transplant (after 2 recurrences treated with the appropriate antibiotics).

Lactose Intolerance

Lactose intolerance is perhaps the single most common potential cause of diarrhea because of the enormously high prevalence of lactase deficiency. This is a disorder so common that the testing and treatment are generally empiric.

The diarrhea produced is associated with gas and bloating, but never contains blood or leukocytes. Despite the malabsorption of lactose, weight loss does not occur.

Diagnosis can be confirmed with increased stool osmolality and increased osmolar gap.

- Osmolar gap means that the difference between the osmolality measure in the stool and the osmolality calculated from the sodium and potassium levels is >50 mOsm/kg.
- Therefore, the measured stool osmolality is greater than would be expected just by the level of sodium and potassium. The extra osmoles are from lactose.
- Other causes of an increased stool osmolar gap are magnesium and polyethylene glycol in the stool, or nutrient malabsorption leading to pancreatic insufficiency, celiac sprue, and bacterial overgrowth.

The routine way to diagnose lactose intolerance is simply to remove milk, cheese, ice cream, and other dairy products (except yogurt) from the diet and observe for resolution of symptoms, which should occur within 24–36 hours. (This differs from celiac disease, where resolution of diarrheal symptoms make take weeks after stopping the ingestion of gluten-containing foods.) If resolution of symptoms does occur, then dietary changes are the best therapy. The patient can use lactase supplements.

Irritable Bowel Syndrome

Although it is often described at the same time as diarrheal illnesses, irritable bowel syndrome (IBS) is predominantly an abdominal pain syndrome with altered bowel habits. The etiology is unknown.

Note

Effective 2018, metronidazole is no longer considered first-line treatment for *C. difficile*. **PO vancomycin or fidaxomicin** is now considered first-line treatment.

IBS is an idiopathic disorder in which there is increased frequency of the normal peristaltic and segmentation contractions of the bowel. Pain is often relieved by a bowel movement.

- 20% of patients have constipation only, while a large percentage have diarrhea alone or diarrhea alternating with constipation.
- Everyone has pain.
- There are no nocturnal symptoms.
- There are no constitutional signs or symptoms, e.g., fever, weight loss, anorexia, or anemia.

Diagnosis. There is no specific diagnostic test for IBS. The first step is to exclude lactose intolerance, IBD, celiac disease, carcinoid, *Giardia* infection, and anatomic defects of the bowel as the cause.

The diagnostic criteria, called Rome criteria, must occur for at least 3 months:

- Pain relieved by a bowel movement or by a change in bowel habit (e.g., when you develop diarrhea, the pain goes away)
- Fewer symptoms at night
- Diarrhea alternating with constipation

Colonoscopy is not needed for diagnosis, but a **work up for celiac sprue must be done if diarrhea is predominant**.

Treatment.

- High-fiber diet to increase bulk of the stool
- Antidiarrheal agent such as loperamide or diphenoxylate for diarrhea-predominant disease
- Hyoscyamine or dicyclomine for abdominal pain
  - Tricyclic antidepressant for IBS-D
  - SSRI for IBS-C
- Osmotic laxative polyethylene glycol for IBD-C; lubiprostone (women) and linaclotide for IBD-C unresponsive to PEG; eluxadoline for abdominal pain and stool consistency in IBS-D; rifaximin for IBS-D

Do not use alosetron due to risk of ischemic colitis.

Carcinoid Syndrome

Carcinoid syndrome describes tumors of the neuroendocrine system. They are most often located in the appendix and ileum. By definition carcinoid syndrome implies metastatic disease (except for bronchial carcinoids). Until there is an enormous tumor burden, the liver is able to neutralize all of the serotonin released by the carcinoid in the bowel. This usually does not happen until the metabolic capacity of the liver has been overwhelmed by metastatic disease.

Bronchial carcinoids are rare but highly symptomatic because the serotonin produced is released directly into the circulation without being detoxified in the liver.

Clinical Presentation. Carcinoid syndrome presents with diarrhea, flushing, tachycardia, and hypotension. A rash may develop from niacin deficiency, a direct result of the carcinoid. Serotonin and niacin are both produced from tryptophan, so if there is an overproduction of serotonin, a tryptophan deficiency (and thus a niacin deficiency) will result. Endocardial fibrosis also occurs because of a constant exposure of the right side of the heart to the serotonin. This leads to tricuspid insufficiency and pulmonic stenosis.

Diagnosis. The diagnosis is confirmed with urinary 5-hydroxyindolacetic acid level (5-HIAA).

Treatment. Therapy is generally based on controlling the diarrhea with octreotide, a somatostatin analog. Very few carcinoids are sufficiently localized to be amenable to surgical resection. If a tumor does happen to be localized, then it should be resected. This is most often possible with bronchial carcinoid. Surgery is also used to relieve obstruction of the bowel.

MALABSORPTION SYNDROMES

The major causes of fat malabsorption are celiac disease and chronic pancreatitis, although in extremely rare cases it is caused by tropical sprue or Whipple disease. What they all have in common is the production of diarrhea characterized as greasy, oily, floating, and fatty, with a particularly foul smell, as if fat were fermenting. This type of diarrhea with fat is called *steatorrhea*.

All malabsorption syndromes are characterized by weight loss because fat has the highest caloric content of all the foods. In addition, there is malabsorption of the fat-soluble vitamins A, D, E, and K.

- Vitamin A deficiency: night blindness (early), complete blindness
- Vitamin D deficiency: hypocalcemia hypophosphatemia, osteomalacia
- Vitamin E deficiency: neuromuscular disorders, hemolysis
- Vitamin K deficiency: prolongation of prothrombin time and easy bruising

Iron malabsorption occurs if there is involvement of the duodenum where iron is normally absorbed. Iron deficiency anemia is evident in all patients with celiac sprue. Macrocytic anemia occurs if folate is malabsorbed. **Vitamin B12 malabsorption** occurs from damage or loss of the mucosal surface of the terminal ileum.

Clinical Presentation. All malabsorption syndromes present with chronic diarrhea. The only unique feature of celiac disease is dermatitis herpetiformis, a vesicular skin rash on the extensor surfaces of the body (10% of patients). Even without dermatitis herpetiformis, celiac disease is the most likely etiology of fat malabsorption because it is the most common.

Chronic Pancreatitis

Chronic pancreatitis is diagnosed with the following:

- History of pain, recurrent attacks of acute pancreatitis, weight loss
- Pancreatic calcifications on imaging
- Exocrine pancreatic insufficiency (steatorrhea)
- Diabetes
- Chronic alcohol abuse (most common cause)

Clinical Pearl

Antibodies Seen in Celiac Disease

- IgA endomysial antibody
- IgA tissue transglutaminase antibody
- IgG tissue transglutaminase antibody

Anti-tissue transglutaminase antibody (IgA) is the most sensitive and specific. In patients with **IgA deficiency**, IgA endomysial and transglutaminase antibodies are **falsely normal**.

Note

In chronic pancreatitis, lipase and amylase are usually normal due to a burnt out pancreas.

If CT does not show calcifications, get MRCP to detect abnormal pancreatic ducts.

For young adults with chronic pancreatitis, work up for cystic fibrosis (especially if there is recurrent pneumonia, sinusitis, and infertility).

Suspect tropical sprue when there is a history of being in a tropical country, and Whipple disease (very rare) if there is dementia (10%) or arthralgia (80%).

Treatment is pancreatic enzymes; pain control with NSAID/acetaminophen, tramadol (may cause hypoglycemia), tricyclic antidepressant, gabapentin, or pregabalin; insulin (required for diabetics, as it mimics type 1 diabetes due to destruction of beta cells).

Do not use narcotics for pain control.

Celiac Sprue

Celiac sprue is secondary to ingestion of wheat, gluten, or related rye and barley proteins. Patients present with the following:

- Chronic diarrhea or steatorrhea
- Bloating, weight loss, abdominal pain
- Pruritic papulovesicular rash on extensor surfaces (dermatitis herpetiformis)
- Isolated abnormalities in liver chemistry tests
- Unexplained iron deficiency anemia (after a negative work up for GI bleed)
- Fat-soluble vitamin deficiencies
- Early onset osteoporosis
- Strong association with type 1 diabetes (should be screened)
- Malabsorption of thyroid hormone in patient with thyroiditis
- IBS-D

Clinical Correlate

Do not let an absence of diarrhea and weight loss keep you from considering celiac. Test for celiac in anyone with unexplained elevation in LFTs or multiple vitamin deficiencies.

The antibodies seen in celiac disease include IgA endomysial antibody, IgA tissue transglutaminase antibody, IgG tissue transglutaminase antibody. **Anti-tissue transglutaminase antibody (IgA)** is the most sensitive and specific. In patients with IgA deficiency, IgA endomysial and transglutaminase antibodies are falsely normal. Check IgG anti-tTG.

Work up celiac in a patient with thyroiditis who is not responding to high doses of levothyroxine.

Diagnosis. Just removing gluten (wheat, rye, oats) from the diet is not an accurate way to establish the diagnosis, because circulating antibodies will be present for weeks after the gluten has stopped.

- First, test for the presence of antiendomysial and anti-transglutaminase antibodies
- Then, small bowel biopsy (**most accurate test**) will show flattening of villi
- Even if antibodies are elevated, do a bowel biopsy to confirm diagnosis and exclude small bowel lymphoma.
- Adherent patients with recurrent malabsorption should be evaluated for intestinal lymphoma.
- Bone mineral testing (for all patients)

An association with IgA deficiency can lead to false-negative IgA-based tests. In patients with IgA deficiency, check IgG-tTG.

Tropical sprue and Whipple disease are diagnosed by finding organisms on a bowel-wall biopsy. The single most sensitive test for Whipple disease is a polymerase chain reaction (PCR) of the bowel biopsy. A positive Tropheryma whippelii biopsy shows foamy macrophages that are PAS positive.

Treatment. Celiac disease is managed by adhering to a gluten-free diet (no wheat, oats, rye, or barley); nonadherence is the most common reason for failure. Use dapsone when celiac patients have dermatitis herpetiformis.

- Trimethoprim/sulfamethoxazole or doxycycline × 6 months (for tropical sprue)
- Trimethoprim/sulfamethoxazole, doxycycline, or ceftriaxone × 1 year (for Whipple disease)

Although all malabsorption syndromes are associated with multiple deficiencies, note some complications:

- Celiac disease is associated with GI lymphoma and adenocarcinoma; there is also high risk for osteoporosis (do a DEXA scan) and streptococcus (give pneumococcal vaccine)
- Celiac sprue is associated with lymphoma (enteropathy-associated T cell lymphoma) (10-15% of cases); unclear whether therapy with gluten-free diet reduces incidence of lymphoma

Note

Celiac patients are at risk for adenocarcinoma of the intestine.

Clinical Recall

A 22-year-old woman complains of intermittent bloating and diarrhea for the past 3 months. Her symptoms are relieved when she avoids her morning coffee and ice cream. On diagnostic testing, her blood and stool tests are within normal limits except for a mild elevation in stool osmolality. What is the most likely cause of her symptoms?

A. Celiac sprue
B. Carcinoid syndrome
C. Irritable bowel syndrome
D. Lactose intolerance
E. Whipple disease

Answer: D

DIVERTICULAR DISEASE

In diverticular disease, small bulges or pockets develop in the lining of the intestine. They often develop where the muscles are weakest, e.g., where penetrating vessels cross through muscle.

Diverticulosis

Diverticulosis is so common in older populations throughout the Western world (50% of persons age >50, with higher rates in older populations) that it is almost considered a normal part of aging. The cause of diverticulosis is believed to a lack of fiber in the diet to give bulk to stool. There is a subsequent rise in intracolonic pressure, leading to outpocketing of the colon.

Clinical Presentation. Most of the time, patients are asymptomatic. When symptoms do exist, they are typically left lower quadrant abdominal pain that is colicky in nature.

Diverticulosis is diagnosed with colonoscopy. Endoscopy is superior to barium study, particularly when bleeding is present. Diverticula are more common on the left in the sigmoid, but bleeding occurs more often from diverticula on the right because of thinner mucosa and more fragile blood vessels. When bleeding occurs from diverticula, it is painless.

Treatment. Treatment is an increased-fiber diet as is found in bran, bulking agents such as psyllium husks, and soluble fiber supplements.

Diverticulitis

Diverticulitis occurs when one of the bulges or pockets (diverticula) becomes infected. This can occur when the diverticular entrance in the colon becomes blocked, perhaps by nuts or corn.

Diverticulitis is distinguished from uninfected diverticula by the presence of fever, tenderness, more intense pain, and elevated white blood cell count.

Diagnosis is confirmed with CT scan. Barium study and endoscopy are contraindicated because there is a slightly higher risk of perforation.

Treatment is antibiotics such as ciprofloxacin and metronidazole. Alternatives are ampicillin/sulbactam, piperacillin/tazobactam, or ertapenem. For mild disease, an oral antibiotic, e.g., amoxicillin/clavulanic acid, can be used. Do colonoscopy 1–2 months after recovery to evaluate.

CONSTIPATION

A 72-year-old woman has a history of upper GI tract bleed and iron-deficiency anemia, for which she has recently been started on oral ferrous sulfate iron replacement. She also has a history of diabetes with peripheral neuropathy, for which she takes amitriptyline. She has untreated hypothyroidism, but is treated for hypertension with nifedipine. Currently, she has constipation, and when the stool does pass it is very dark in color, almost black.

The most common cause of constipation is lack of dietary fiber and insufficient fluid intake. CCBs, oral ferrous sulfate, hypothyroidism, opiate analgesics, and medications with anticholinergic effects such as the tricyclic antidepressants all cause constipation. In the patient, the most likely cause of the constipation is the ferrous sulfate.

- Very dark stool, as in this patient, occurs only with bleeding, bismuth subsalicylate ingestion, and iron replacement.
- However, GI bleed produces diarrhea—not constipation—because blood acts as a cathartic.
- Blood causes diarrhea, and iron tablets cause constipation.

Treatment. Stop all medications that cause constipation; then make sure the patient stays well-hydrated and consumes 20–30 grams of daily fiber.

- Bulking agents, such as those used to manage diverticular diseases
- Drug treatment: milk of magnesia, cascara, bisacodyl, docusate
- Enema (acute and serious constipation)
- Lactulose and polyethylene glycol

COLON CANCER

The lifetime risk of colon cancer is >6%. Most cases occur sporadically, which is to say there is no clearly identified etiology.

A diet high in red meat and fat leads to an increased risk, as does smoking.

- When the cancer is in the right side of the colon, patients present with heme-positive brown stool and chronic anemia.
- When the cancer is in the left side or in the sigmoid colon, patients present with obstruction and narrowing of stool caliber; that is because the right side of the colon is wider than the left, and the stool is more liquid in that part of the bowel, making obstruction less likely on the right.
- Endocarditis by *Streptococcus bovis* and *Clostridium septicum* have a strong association with colon cancer. Anyone presenting with endocarditis due to one of these organisms requires a GI work-up.

Diagnosis. Colonoscopy is the most accurate diagnostic test. Sigmoidoscopy will reach the lesion only within the distal 60 cm of the colon. If the lesion is in the distal area then the sigmoidoscopy will be equally sensitive as colonoscopy, but only 60% of cancers occur there. Barium study is not as accurate as colonoscopy, nor can you biopsy.

Treatment. Treatment depends on the stage of disease and extent of its spread.

- Single liver metastatic lesion: surgical resection
- Cancer localized to the mucosa, submucosa, and muscularis layers: surgical resection; curable
- Cancer penetrated to the serosa and spread into surrounding tissue and lymph nodes: surgical resection not effective in eradicating disease
- Widespread disease: chemotherapy (mainstay of chemotherapy for GI malignancies such as colon cancer is 5-fluorouracil [5FU])

Screening should occur in the general population after age 50, as per the following recommendations.

- High-sensitivity fecal occult blood testing (FOBT) or fecal immunochemical test (FIT) every year
- Flexible sigmoidoscopy every 5 years
- Flexible sigmoidoscopy every 10 years with annual FIT **or** colonoscopy every 10 years
- CT colonography every 5 years

If adenomatous polyps were found on previous colonoscopy, repeat colonoscopy in 3–5 years. In cases of family history of colon cancer, begin screening at age 40 or 10 years earlier than the family member got cancer, whichever is younger (also see Preventive Medicine chapter).

After polypectomy, intervals for follow-up colonoscopy are as follows:

- **Small rectal hyperplastic polyp**: every 10 years
- **1–2 small (<1 cm) tubular adenomas**: every 5 years
- **3–10 adenomas, any adenoma >1 cm, or adenoma with high-grade dysplasia or villous**: every 3 years
- **>10 adenomas**: every <3 years (consider familial syndromes)
- **Large (>2 cm) (size does matter) sessile polyp removed by piecemeal excision**: every 2–6 months
- **Polyp with adenocarcinoma** (minimal invasion and >2 mm margin): every 2–3 months

Hereditary Nonpolyposis Syndrome (Lynch Syndrome)

Certain families carry a genetic defect with a high degree of penetrance for colon cancer. The genetic defect does not cause polyps, however. By definition, the syndrome is defined as:

- Three family members in at least 2 generations with colon cancer
- One of these cases should be premature, i.e., occurred in someone age <50

Patients with this syndrome are also at increased risk for ovarian and endometrial cancer (up to 30%).

Screening. Start screening at age 25 and undergo colonoscopy every 1–2 years.

Hereditary Polyposis Syndromes

Familial adenomatous polyposis has a very clear genetic defect. The adenomatous polyposis coli gene (APC) confers 100% penetrance for the development of adenoma by age 35 and of colon cancer by age 50. Polyps can be found as early as age 25.

- Start screening at age 10–12 and do flexible sigmoidoscopy every 1–2 years.
- As soon as polyps are found, perform a colectomy; a new rectum should be made from the terminal ileum.
- Do upper endoscopy screening for duodenal cancer at the onset of colonic polyposis or age 25–30, whichever comes first.

By contrast, **juvenile polyposis syndrome** confers about a 10% risk of colon cancer. There are only a few dozen polyps, as opposed to the thousands of polyps found in those with familial polyposis. In addition, the polyps of the juvenile polyposis syndrome are hamartomas, not adenomas. Hamartomas confer very little risk of developing into cancer. There is no specific recommendation for screening.

Cowden syndrome is another polyposis syndrome with hamartomas that gives only a slightly increased risk of cancer compared with the general population. These polyposis syndromes can present with rectal bleeding in a child.

Other Polyposis and Colon Cancer Syndromes

Gardner syndrome is the association of colon cancer with multiple, soft-tissue tumors, such as osteomas, lipomas, cysts, and fibrosarcomas. Osteomas are frequently found on the mandible. If osteomas are found as an incidental finding on x-ray, do a colonoscopy.

Note

If osteomas are seen as an incidental finding on x-ray, perform a colonoscopy.

Peutz-Jeghers syndrome is the association of hamartomatous polyps in the large and small intestine with hyperpigmented spots. These are melanotic spots on the lips, buccal mucosa, and skin. The risk of cancer is slightly increased above the general population. Most common presentation is with abdominal pain due to intussusception/bowel obstruction.

Turcot syndrome is simply the association of colon cancer with CNS malignancies.

Screening. There is no recommendation for increased cancer screening for any of these syndromes; they are not common enough to warrant a clear recommendation for uniform early screening. There is an association of endocarditis from *Streptococcus bovis* with colon cancer, so if a patient has endocarditis from *S. bovis*, colonoscopy should be performed.

GASTROINTESTINAL BLEEDING

A 72-year-old man with a history of aortic stenosis is brought to the ED with red/black stool several times today. His blood pressure is 94/60 mm Hg and pulse 110/min.

With GI bleed, **treat before you investigate the etiology**.

- **Upper GI bleed** causes include:
  - Ulcer disease
  - Gastritis
  - Mallory-Weiss syndrome
  - Esophagitis
  - Gastric cancer
  - Aortoenteric fistula (consider if there is a history of abdominal aortic aneurysm repair in past 6–12 months
  - Variceal bleed, common in those with portal hypertension from cirrhosis

Note

Upper GI bleed is defined as bleeding occurring proximal to the ligament of Treitz, which anatomically separates the duodenum from the jejunum.

Note

Orthostasis is defined as a >10-point rise in pulse when patient goes from supine to standing or sitting OR a >20-point drop in systolic BP on a change in position.

- At least 1 minute must pass between the position change and the measurement of pulse/BP, to allow the normal autonomic discharge to accommodate to the position change.
- In the vignette described here, the measurement of orthostatic changes is not necessary because pulse >100/min or systolic BP <100/min already indicates a >30% blood loss.

Note

- Occult blood–positive brown stool can occur with as little as 5–10 mL of blood loss.
- Melena can occur with ≥100 mL of blood loss.

Note

Virtual endoscopy is a CT scan used to try to detect cancer without the need of endoscopy. It lacks both sensitivity and specificity to detect causes of GI bleed.

Do not use for this purpose.

- **Lower GI bleed** causes include:
  - Diverticulosis
  - Angiodysplasia (also known as AVM or vascular ectasia)
  - Hemorrhoids
  - Cancer
  - IBD
  - Iron deficiency (slow and chronic bleeding)

Clinical Presentation.

- **Upper GI bleed**: generally black stool or melena
  - Bright red blood per rectum in 10% of cases
  - Elevated BUN/creatinine ratio if volume of bleeding is very high (so high that it is rapidly transported to the bowel without time to oxidize and turn black)
  - Orthostasis (pulse or drop in BP persists after one's position has changed), which indicates a 15–20% blood loss
- **Lower GI bleed** more commonly presents with red blood in the stool

Diagnosis.

- Endoscopy (**most accurate test to determine etiology**); occasionally, endoscopy will not reveal the etiology of lower GI bleeding, even during an active bleed
- Barium study (less accurate)
- Biopsy if needed, but do endoscopy first
- Nuclear bleeding scan for low volume bleeds 0.1–0.5 mL/min; RBCs from the patient are tagged with technetium, reinjected back, and then detected to determine the site of bleeding
- Angiography
  - Requires a higher volume of blood loss >0.5 mL/min compared with the nuclear scan
  - Used in extremely high-volume bleeding when so much blood is coming out that endoscopy cannot see the source
  - May then be used prior to embolization of the site of the bleeding or hemicolectomy
  - Can help guide the occasional use of a local vasopressin injection in the control of severe lower GI bleeding

Obscure GI bleeding is recurrent blood loss without an identified source. It could be a tumor, Crohn disease, or angiodysplasia (40%). Patients may have melena or hematochezia or positive FOBT.

- The first step is to repeat the upper endoscopy and/or colonoscopy (diagnostic in 25%). (This should be done before capsule endoscopy.)
- For active obscure GI bleeding, perform nuclear studies followed by angiography. If unrevealing, perform push enteroscopy or balloon-assisted enteroscopy.
- The newest modality to visualize the small bowel with occult bleeding is capsule endoscopy; the patient swallows a capsule containing an electronic camera which then transmits thousands of images to a nearby receiver and allows anatomic localization of the lesion.

Treatment must start with fluid resuscitation using normal saline or Ringer's lactate. Complete blood count, prothrombin time, and type and crossmatch should be done, but if the patient is having a high volume bleed, do not wait for the test results to begin fluid resuscitation.

- Prothrombin concentrate complex if prothrombin time is elevated
- IV vitamin K if on warfarin, to replace fresh frozen plasma
- Platelet transfusion if platelets <50,000/mm^3 and patient is actively bleeding
- IVFs to keep HR <100/min and systolic BP >100 mm Hg
- Blood transfusion if there is hemodynamic instability or hemoglobin <7 g/dL
- IV PPI
- Upper endoscopy within 24 hours (within 12 hours for variceal bleeding)
- Do not use a nasogastric tube

For **acute bleeding**, additional treatment is as follows:

- Octreotide to lower portal pressure
- Antibiotics (ceftriaxone or ciprofloxacin) to prevent systolic BP rise, even if there is not ascites (**high yield for the exam**)
- If banding is not effective in stopping an acutely bleeding esophageal varix, then perform TIPS (transjugular intrahepatic portosystemic shunting); the most common long-term complication of TIPS is worsening of hepatic encephalopathy
- Blakemore tube to tamponade the site of bleeding in the stomach or esophagus (rarely used) is only a temporary bridge to surgery

Propranolol is a nonselective beta-blocker used in the long-term management of portal hypertension to decrease the frequency of bleeding. Everyone with varices from portal hypertension and cirrhosis should be on a beta-blocker.

Low risk ulcers are clean-based or have nonprotuberant pigmented spots; treat with oral PPIs, full diet and early hospital discharge (12 hours).

High risk ulcers have active arterial spurting or nonbleeding visible vessel or adherent clot. Treat endoscopically with hemo-clips, thermal therapy, or epinephrine injection; clear diet for 48 hours; and IV PPI infusion for 72 hours.

Clinical Recall

Which of the following colonic conditions requires additional colonoscopy screening?

A. Cowden syndrome

B. Gardner syndrome

C. Juvenile polyposis syndrome

D. None of the above

Answer: D

Note

H2 blockers are not helpful with GI bleed.

Note

In the TIPS procedure, a catheter is placed into the jugular vein and guided radiographically through the liver. The goal is to form a shunt between the systemic circulation in the hepatic vein and the portal circulation through the portal vein.

TIPS has largely replaced the need to surgically place the shunt.

Note

Lower GI bleeding presents with red blood in the stool, whereas **upper GI** bleeding usually presents with black stool.

PANCREATITIS

Acute Pancreatitis

Acute pancreatitis is inflammation of the pancreas due to premature activation of trypsinogen into trypsin while still in the pancreas (common pathway of most causes of pancreatitis). This results in autodigestion of the pancreas. Circulating cytokines can lead to many complications.

Most cases of pancreatitis are caused by alcoholism and gallstones. Other causes include:

- Medications such as valproate, pentamidine, didanosine, azathioprine, and sulfa derivatives, e.g., sulfamethoxazole/trimethoprim and thiazide diuretics
- Hypercalcemia
- Hypertriglyceridemia, where elevated triglycerides are broken down to fatty acids, causing inflammation of the biliary tract and eventual pancreatitis
- ERCP, presumably because of back pressure from injection of the contrast material into the ductal system; most patients who have pancreatic injury from ERCP have just an asymptomatic increase in amylase
- Trauma and various viruses, such as mumps

Clinical Presentation. Midepigastric pain with tenderness and nausea/vomiting. The pain typically radiates straight through to the back.

When extremely severe, pancreatitis can mimic many of the features of septic shock, with fever, hypotension, respiratory distress from ARDS, elevated WBCs, and a rigid abdomen.

Diagnosis. To diagnose, 2 of the following 3 features must be present:

- Acute onset of upper abdominal pain
- Amylase or lipase >3× the upper limit of normal
- Evidence on imaging

The initial tests remain as amylase and lipase (lipase is more specific to the pancreas than amylase). CT scan should not be given routinely; only do if pancreatitis is severe, lasts longer than 48 hours, or complications are suspected.

Hypertriglyceridemia can give falsely normal amylase and lipase levels.

The most important sign of severe pancreatitis and poor prognosis is elevated or rising BUN.

- **CT scan**: most accurate test for determining severity; the APACHE score is also used to stratify acute pancreatitis
- **ERCP**: most accurate test for detecting biliary and pancreatic ductal pathology

Treatment is aggressive IV fluids (250–500 mL/hr), bowel rest, and pain medication. Use morphine, as it does not constrict the sphincter of Oddi, and never use meperidine (can cause seizures).

- Aggressive IV fluids are most beneficial in first 12–24 hours and may be harmful after that time; reduce after 24 hours (Lactated Ringer's is preferred over normal saline based on clinical data).
- Resume oral feeding as soon as pain and nausea resolve; no need to wait.

Clinical Pearl

Always consider gallstone pancreatitis and rule it out by U/S, even in patients with history of alcohol use.

Note

Signs of Severe Necrotizing Pancreatitis

Cullen sign: blue discoloration around umbilicus → due to hemoperitoneum

Turner's sign: bluish purple discoloration of the flanks → tissue catabolism of Hb

Note

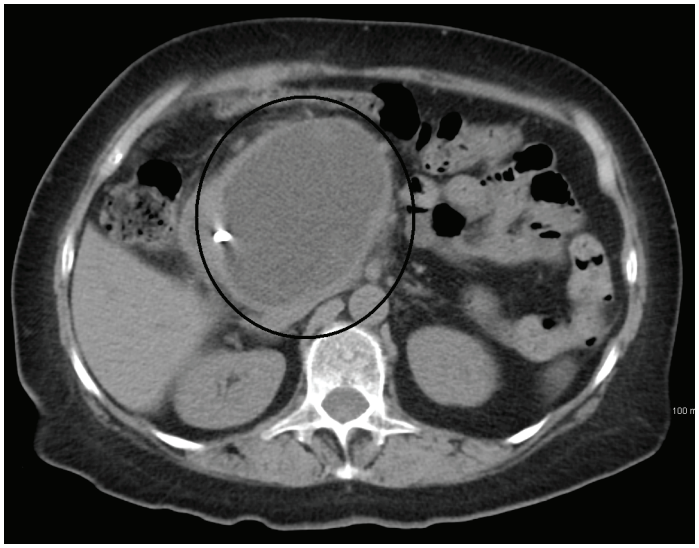
CT is more accurate than sonogram for detecting inflammation, necrosis, pseudo-cysts, abscesses, and ductal stones.

- Administer antibiotics only if evidence of infected necrosis based on biopsy; do not give antibiotics for necrosis without infection.
- Do ERCP only if ascending cholangitis or nonresolving biliary obstruction, as it can otherwise worsen pancreatitis.

For gallstone pancreatitis, do cholecystectomy prior to discharge.

For severe acute pancreatitis that does not resolve within 72 hours, give enteral feeding via NGT or nasojejunal feeds, not total parental nutrition. Data shows that enteral feeding improves mortality (vs parental). Do not keep patient NPO after 72 hours, as that leads to increased risk for sepsis and death.

- When pancreatitis is very severe, e.g., >30% necrosis visible on CT, the risk of infected and hemorrhagic pancreatitis markedly increases.
- Severe necrosis, particularly when there is persistent fever, is also an indication to perform a percutaneous needle biopsy of the pancreas. If infection of the pancreas accompanies the necrosis, imipenem and urgent surgical debridement are indicated.
- Antibiotics should not be routinely given for pancreatic necrosis; they should be reserved for those with proven infection.
- If patient does not improve or deteriorates 7–10 days after presentation, perform CT-guided fine-needle aspiration.
- In stable patients with infected necrosis, the preferred approach is to initiate antibiotics and to ideally delay drainage procedures for at least 4 weeks to allow the collection to become encapsulated, which facilitates drainage.
- Pseudocysts develop only 2–4 weeks after the episode of pancreatitis; drain them if there is pain, fistula formation, or rupture (asymptomatic pseudocysts need not be drained).



Wikipedia, James Heilman, MD

Figure 4-3. Pancreatic Pseudocyst

Note

Other complications of pancreatitis include:

- Ascites (high in amylase)
- Pleural effusion (transudate, increased amylase)
- Splenic vein thrombosis (think when there are gastric varices but no esophageal varices)

Autoimmune Pancreatitis

Autoimmune pancreatitis is an autoimmune condition involving the pancreas and bile duct. Men > women.

Type I presents with painless jaundice or acute pancreatitis (rare).

- 'Sausage-shaped' pancreas on CT
- Older man
- Elevated IgG4

IgG4-related disease (IgG4-RD) is a chronic inflammatory condition characterized by tissue infiltration with lymphocytes and IgG4-secreting plasma cells causing various degrees of fibrosis (scarring) involving multiple organs.

Multiple autoimmune conditions are seen, including Sjögren syndrome, primary sclerosing cholangitis, hepatomegaly interstitial nephritis (enlarged kidneys), and inflammatory bowel disease.

Type II presents with chronic pancreatitis.

- No systemic disease
- Normal IgG4
- Need biopsy to diagnose

Treatment is steroids.

Note

While alcohol is the most common cause of cirrhosis in the United States, the most common reason to need a liver transplant is chronic hepatitis C.

LIVER DISEASE AND CIRRHOSIS

Cirrhosis develops when there is chronic and severe inflammation of the liver for an extended period of time. The regenerative capacity of the liver is enormous; however, over a long time, fibrosis will develop. And when at least 70–80% of liver function has been lost, the synthetic capacity of the liver is diminished.

In the United States the most common cause of cirrhosis is alcohol. Other causes include primary biliary cirrhosis, sclerosing cholangitis, alpha-1 antitrypsin deficiency, hemochromatosis, and Wilson disease.

The complications of cirrhosis are due to portal hypertension. Portal hypertension develops because of mechanical factors of fibrosis and regenerative liver nodules, as well as increased intrahepatic vascular resistance in increased portal inflow. The high pressure in the portal vein is decompressed through collateral portosystemic shunts that occur in the esophagus and the stomach.

Note

- All of the clotting factors are made in the liver—except for factor VIII and von Willebrand factor, made by endothelial cells.
- If factor VIII is low in addition to other factors, it is not liver disease—think disseminated intravascular coagulation (DIC).

Clinical Presentation. Despite the etiology, all forms of cirrhosis have the following features:

- Low albumin
- Portal hypertension
- Esophageal varices
- Ascites (the result of portal hypertension)
- Peripheral edema

- Elevated prothrombin time (prolonged due to loss of ability to synthesize clotting factors)
- Splenomegaly
- Thrombocytopenia
- Spider angiomata
- Palmar erythema
- Asterixis
- Encephalopathy (possible)
- Jaundice (possible)

A paracentesis is a sample of the ascitic fluid obtained by needle through the anterior abdominal wall. A paracentesis is used to exclude infection, as well as to determine the etiology of the ascites if it is not clear from the history.

Spontaneous bacterial peritonitis (SBP) is an idiopathic infection of ascites. The Gram stain is rarely positive because the density of microorganisms is so low. Although culture of the fluid is the most specific test, do not wait for the results to make a decision as to whether to give antibiotics.

- Neutrophils >250/mm^3 are the criteria for the presence of infection
- Treatment is cefotaxime or ceftriaxone; albumin infusion can help to reduce the risk of hepatorenal syndrome
- Once a patient has SBP, the risk of recurrence is 70% per year; give norfloxacin or ciprofloxacin daily (indefinitely) to prevent recurrence
- Stop all beta-blockers due to increased mortality

Serum-AscitesAlbumin Gradient. Normally, the ascitic fluid albumin level is less than the serum level. The **difference between them** is referred to as the serum-ascites albumin gradient (SAAG). Total protein in the ascites fluid must also be checked.

When SAAG ≥1.1, portal hypertension, the cause of ascites is increased hydrostatic pressure. The ascites total protein will tell you the cause of the elevated hydrostatic pressure.

- When SAAG ≥1.1 and total protein <2.5 g/dL, the portal hypertension is due to cirrhosis (liver produces less protein due to decreased function).
- When SAAG ≥1.1 and total protein >2.5 g/dL, heart failure, Budd-Chiari (check JAK2 to work up P. vera).

When SAAG <1.1, it means the ascitic fluid albumin level is high. Cancer and infections generally produce SAAG <1.1.

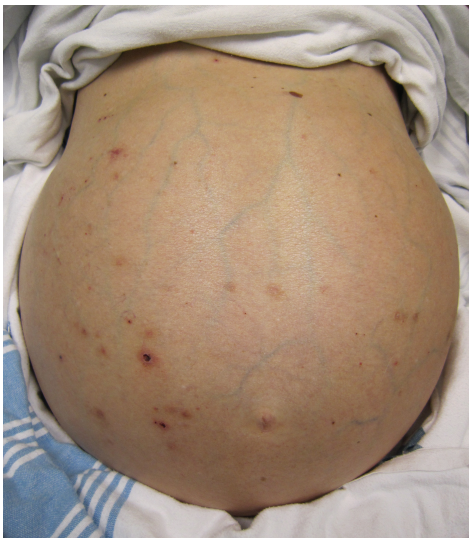
- When SAAG <1.1 and total protein <2.5 g/dL, there is nephrotic syndrome (protein is lost in urine).
- When SAAG <1.1 and total protein >2.5 g/dL, there is carcinomatosis (think ovarian), Tb (do peritoneum biopsy, which will have high lymphocytes in ascites, too)

Note

Although a culture of the ascitic fluid is the most specific test for SBP, do not wait for culture results when considering antibiotics.

Clinical Pearl

Remember to subtract the lower number (ascites albumin) from the higher number (serum albumin) when calculating SAAG.



Wikipedia, James Heilman, MD

Figure 4-4. Ascites

Note

For HCC, do U/S screening every 6 months.

Treatment. There is no specific therapy to reverse cirrhosis; one can only manage the complications and treat the underlying causes. (A complication to consider is hepatocellular carcinoma.) Edema and fluid overload in third spaces, such as ascites, are managed with diuretics (spironolactone most useful in cirrhosis). That is because cirrhotics have intravascular volume depletion, producing a high aldosterone state (secondary hyperaldosteronism). Furosemide is commonly added after spironolactone to increase volume removal. Giving furosemide without spironolactone will lead to hypokalemia, which can cause encephalopathy.

Propranolol is used to prevent bleeding in portal hypertension and varices. Discontinue after SBP, refractory ascites, or hypotension.

Encephalopathy is managed with lactulose, a nonabsorbed disaccharide that bacteria metabolize in the colon, making it more acidic. This converts the NH3 to NH4+, or ammonia to ammonium. Ammonium is not absorbed very well, and that leads to an overall increased excretion of ammonia from the body.

If patient is not responsive, add rifaximin, an RNA polymerase blocker not absorbed which changes the flora of the GI tract. Neomycin is not used for encephalopathy due to renal toxicity.

Note

Give octreotide during a bleed, then band. Give propranolol after the bleed to prevent another bleed.

Hepatorenal syndrome is diagnosed by the following:

- Increased creatinine >1.5 mg/dL over days to weeks
- Lack of response to albumin infusion for 48 hours (stop diuretics, too)
- Exclusion of other causes of AKI (sepsis); must have normal urine (no blood or protein)
- Type 1 is more severe with doubling of creatinine in 2 weeks.
- Type 2 is less severe with more gradual increase in creating.

Treat with midodrine, octreotide and albumin (must give for 48 hours first to rule out prerenal). If it fails, perform liver transplant.

Although vitamin K is often given because of the elevated prothrombin time, it is not effective because the liver is unable to synthesize clotting factors regardless of how much vitamin K is present.

Note

In a patient with ascites, stop ACE-I, ARBs, and NSAIDs.

Primary Biliary Cirrhosis

Primary biliary cirrhosis is an idiopathic autoimmune disorder that is often seen in middle-aged women. Bilirubin does not elevate until the disease is extremely far advanced (5–10 years). There is a strong association with other autoimmune diseases, such as Sjögren syndrome, rheumatoid arthritis, and scleroderma.

Clinical Presentation. The most common symptoms are fatigue and pruritus. At least 30% of patients are asymptomatic but are found to have an elevated alkaline phosphatase when measured for other reasons. Osteoporosis and hypothyroidism are found in 20–30% of patients.

Diagnosis. The transaminases are often normal. The most common abnormality is elevated alkaline phosphatase and gamma glutamyl transpeptidase (GGTP). Total IgM levels are also elevated. The most specific blood test is the antimitochondrial antibody.

Biopsy is always the best way to diagnose liver disease. It is the only test more specific than antimitochondrial antibodies.

Treatment. There is no specific therapy for primary biliary cirrhosis. Steroids will not help. Ursodeoxycholic acid is primary treatment. Cholestyramine will help with the pruritus, as will ultraviolet light. Liver transplant for late stage PBC may also be considered.

Primary Sclerosis Cholangitis

Primary sclerosis cholangitis is an idiopathic disorder of the biliary system most commonly associated with IBD. Although it is more often found with ulcerative colitis, it can also occur with Crohn disease. Cancer of the biliary system can develop in 15% of patients from the chronic inflammation.

Note

Primary sclerosis cholangitis is the only chronic liver disease in which a **liver biopsy is not the most accurate test.**

Clinical Presentation and **Diagnosis.** The presentation and general lab tests are typically the same as those for primary biliary cirrhosis, except that the antimitochondrial antibody test will be negative. The most specific test for primary sclerosis cholangitis is ERCP or MRCP: "string of beads of MRCP or ERCP." This is the only chronic liver disease in which a liver biopsy is not the most accurate test.

Treatment. Treat with endoscopic therapy for strictures; cholestyramine for itching.

Hemochromatosis

Hemochromatosis is one of the most common inherited genetic diseases. There is an overabsorption of iron in the duodenum, leading to iron buildup in tissue throughout the body, thus resulting in chronic hepatic inflammation and fibrosis. Presentation includes the following:

- Cirrhosis (most common finding)
- Hepatocellular cancer (15–20% of patients)
- Restrictive cardiomyopathy (15% of patients)

Note

Ferritin is elevated in liver disease and alcoholics. **Transferrin saturation** is the best screening test; if it is **negative**, **diagnosis is not hemochromatosis**.

- Arthralgias, **osteoarthritis in the MPC joints, osteophytes on x-ray**, skin hyperpigmentation, diabetes, and secondary hypogonadism (decreased libido and impotence)
- *Vibrio vulnificus* and *Yersinia* infections occur with increased frequency because of their avidity for iron.

Screening for hemochromatosis is made with elevated transferrin saturation >55%. Ferritin is also elevated. C282Y homozygous and C282Y/H63D are diagnostic of hemochromatosis and do need a liver biopsy for diagnosis.

The most accurate test is a liver biopsy.

Treatment. Phlebotomy is used to remove large amounts of iron from the body—it removes far more iron than do the chelating agents deferoxamine and deferasirox. Deferoxamine and deferasirox are used only for those who cannot undergo phlebotomy.

Wilson Disease

Wilson disease is an autosomal recessive disorder leading to a diminished ability to excrete copper from the body. There is also increased copper absorption from the small intestine.

- Copper builds up in the liver, brain, and cornea.
- Basal ganglia dysfunction contributes to the movement disorder which develops.
- Psychiatric disturbance is seen in 10% of patients.
- Kayser-Fleischer rings are found in the eye on slit-lamp examination.
- Tremor and Parkinson result in 35% of patients.
- Fanconi syndrome and type II proximal renal tubular acidosis develop due to copper deposition in the kidney.
- Hemolytic anemia may be present (copper destabilizes the RBC membranes).

Note

A patient presenting with choreoathetoid movements and psychosis gives the clue to perform the slit-lamp examination. Kayser-Fleischer rings are then found, confirming the diagnosis of Wilson disease.

The most specific blood test for diagnosis is decreased ceruloplasmin but that alone is not enough. There is also increased urinary copper. The single most specific test is liver biopsy, which will demonstrate increased copper deposition in the liver. Occasionally, hemolytic anemia is seen when copper levels go high and are toxic to the red cells.

Treatment. Penicillamine and trientine are copper chelators. Oral zinc interferes with copper absorption. Steroids will not help. Liver transplantation is curative.

Alpha-1 Antitrypsin Deficiency

Alpha-1 antitrypsin deficiency (AATD) is an autosomal recessive condition which causes a low level (or no level) of alpha-1 antitrypsin (AAT) in the blood. The condition is found in all ethnic groups but occurs most often in whites of European ancestry. AAT protects the lungs so they can have normal function. AAT is made in the liver; without enough of it, the lungs become damaged, leading to emphysema.

- Everyone has 2 copies of the gene for AAT and receives 1 copy of the gene from each parent.

- Patients with AATD have 1 normal copy and 1 damaged copy, or they have 2 damaged copies.
  - Most patients with 1 normal gene can produce enough AAT to live healthy lives, especially if they do not smoke.
  - Those with 2 damaged copies of the gene are generally not able to produce enough AAT, leading them to have more severe symptoms.

The most prominent finding is emphysema developing at a young age in a nonsmoker. Approximately 15% of those with AATD develop cirrhosis. Large amounts of abnormal AAT are made in the liver; nearly 85% of this protein accumulates in the liver causing inflammation and eventually, fibrosis.

Diagnosis. Testing for AATD using a blood sample from the individual is simple, quick and highly accurate. Three types of tests are usually done on the serum sample:

- Alpha-1 genotyping, which examines a person's genes and determines his genotype
- AAT PI type of phenotype test, which determines the type of AAT protein a person has
- AAT level test, which determines the amount of AAT in a person's blood

Treatment. There is no specific therapy for the liver disease. Those with emphysema should receive replacement of the enzyme and stop smoking.

Chronic Hepatitis B and C

Hepatitis B and C are transmitted by blood products, needlestick injury, and sexual contact. Injection drug use is also strongly associated with both viruses.

- Hepatitis C virus causes 60–70% of cases of chronic hepatitis; at least 80% of acute hepatitis C cases become chronic
- About 10% of hepatitis B cases, sometimes with hepatitis D coinfection, become chronic; hepatitis D does not occur by itself but rather only as a coinfection with hepatitis B
- Rarely, hepatitis E virus causes chronic hepatitis in those with weakened immune systems (organ transplant treatment, chemotherapy for cancer, HIV infection)
- Hepatitis A virus does not cause chronic hepatitis

Hepatitis C is the most common cause of chronic hepatitis in the United States; it is also the most common cause of cirrhosis and hepatocellular carcinoma.

Most patients are asymptomatic until the disease is very far advanced.

Diagnosis.

- To **confirm hepatitis B**: persistence of hepatitis B surface antigen >6 months (though it takes years for cirrhosis to develop)
  - Remember, in **chronic hepatitis B, the hep B surface antibody is negative**.
- To confirm hepatitis C: finding an antibody to hepatitis C, and then finding an elevation of the viral load by PCR methods
  - Single most accurate test to diagnose the extent of liver disease is liver biopsy

Treatment. Chronic hepatitis B is treated with interferon, lamivudine, entecavir, telbivudine, or adefovir. Combining these agents does not lead to increased efficacy.

Chronic hepatitis C is now cured with the new combination antiviral drugs. The most commonly used is **ledipasvir/sofosbuvir** (trade name **Harvoni**), a 2-drug combination. It is administered as a 1×/daily pill containing the viral NS5A inhibitor ledipasvir and a nucleotide inhibitor of the viral RNA polymerase, sofosbuvir. Taken daily for 8–12 weeks, it provides cure rates of 94–99% in those infected with genotype 1 (the most common form of hepatitis C in the United States and some European countries), irrespective of the presence or absence of liver cirrhosis or prior unsuccessful treatment. It has also been evaluated for the treatment of infection with other hepatitis C genotypes and has shown promising results in genotypes 3 and 4.

Clinical Recall

Which of the following is not a cause of cirrhosis?

A. Alpha-1 antitrypsin deficiency

B. Budd-Chiari syndrome

C. Hepatitis A

D. Hemochromatosis

E. Primary biliary cirrhosis

Answer: C

Cardiology 5

Learning Objectives

- Outline a differential diagnosis and diagnostic plan for patients with acute chest pain or chest discomfort
- List the causes of and treatment for heart rate and rhythm disturbance
- Describe the physiology of valvular disease and CHF, and describe the mechanism of action of appropriate treatments
- Give an overview of presentation, epidemiology, and management of ischemic heart disease, acute coronary syndrome, myocardial disease, and pericardial disease
- Describe the most common medications used to treat cardiovascular disease and their most serious or common side effects

ACUTE CHEST PAIN

Chest pain or discomfort is one of the most common complaints that brings patients to the physician's office or ED. Patients presenting with this symptom may have an underlying cause that is benign and requires only moderate analgesic medication or is life-threatening (e.g., acute myocardial ischemia or aortic dissection) which mandates prompt diagnosis and treatment.

In the evaluation of chest pain, the focus should be on **excluding the more serious conditions**.

History

Assessing the setting in which the chest pain occurs is one of the most important aspects of the evaluation. The healthy 26-year-old medical resident with chest pain that occurred after on-call is unlikely to have cardiovascular disease, no matter the quality or duration of chest pain. The 58-year-old man who has type 2 diabetes and dyslipidemia with chest discomfort of any type has a much higher probability for cardiac-related chest pain.

Overall, the **chest pain history is more useful than the physical examination**. Important aspects of the history include duration, quality, location, radiation, frequency, alleviating or precipitating factors (especially exercise), and associated symptoms.

- For both stable angina and acute coronary syndromes, the quality of chest pain is described by the patient as "tightness," "heaviness," or "pressure," but symptoms resembling acute abdomen (pain in upper abdomen, nausea) are not uncommon. Nausea and vomiting are sometimes the main symptoms in inferoposterior wall ischemia (also, vagal reflexes may cause bradycardia and hypotension, presenting as dizziness or fainting).
- "Sharp" or "knife-like" chest pain and pain which the patient can pinpoint to an "exact area" are less likely to be related to ischemia or infarction, especially if the chest pain is reproduced by changes in position or palpation.
- Myocardial infarction (MI) is associated with pain that lasts >20–30 minutes in duration.
- Response of chest pain to nitroglycerin (within a few minutes) is most consistent with transient ischemia or esophageal spasm. Chest pain that worsens with nitroglycerin sometimes occurs with gastroesophageal reflux disease. The response to nitroglycerin is not enough to confirm coronary disease as the cause of chest pain.
- Acute coronary syndromes in women often present without "classic" symptoms: instead, they may have dyspnea, shortness of breath, fatigue.

Physical Examination

One of the most important parts in a chest pain examination is the "initial impression."

- Diaphoresis, tachypnea, and anxious expression should alert you to a potentially life-threatening process.
- Tachycardia and tachypnea are both nonspecific but occur in almost all cases of pulmonary embolism.
- Check BP in both arms: a difference >20 mm Hg systolic suggests aortic dissection (present in ~70% of cases).
- Hypotension may suggest massive pulmonary embolism or cardiac shock.
- Fever may suggest pneumonia or mediastinitis (esophageal rupture) as the cause of chest pain.
- Evidence of atherosclerosis (corneal lipid rings, narrowed retinal arteries, and pigment and hair changes in the legs) is commonly seen in patients with coronary syndromes.

Inspect the chest wall for tender areas, respiratory motion, respiratory retractions, or accessory muscle use. If the tender area corresponds to the location of the patient's pain and palpation exactly reproduces the pain, consider musculoskeletal chest pain as the cause of chest pain.

Abnormal heart sounds and new murmurs are commonly found in certain chest pain syndromes.

- Wide physiologic splitting of the second heart sound (splitting wider with inspiration) can be found in right bundle branch block or in right ventricular infarction.
- New paradoxical splitting is most often due to left bundle branch block (LBBB), or anterior or lateral infarction.
- A new fourth heart sound can occur with angina or infarction. An S3 is more likely due to underlying heart failure.
- A new murmur may be significant: aortic regurgitation occurs in over half of patients with aortic dissection, while mitral regurgitation can occur in patients with angina or infarction and is due to papillary muscle dysfunction.

The lungs should be auscultated for crackles and asymmetrical breath sounds. Asymmetry of breath sounds may be found in patients with spontaneous pneumothorax. Absent lung sounds also may occur in pneumothorax and pleural effusions.

The extremities should be examined for pulses, edema, and signs of atherosclerotic vessel disease. Absence of pedal pulses may occur in aortic dissection. Calf swelling or edema raises the odds of pulmonary embolism as the cause of chest pain.

Testing

All patients with chest pain should have a 12-lead ECG (**most important test**) to evaluate the cause. It should be done immediately after initial stabilization and taking of vital signs. In patients with acute coronary syndromes, the ECG is the sole test required to select patients for emergency reperfusion.

Most patients with MI will have an abnormal initial ECG:

- 50% with acute MI will have diagnostic findings (ST elevation, new LBBB, or Q waves)
- 35% will have findings consistent with ischemia (ST depression and/or T wave inversion)
- In patients presenting with acute chest pain who have **normal ECG**, the chance of acute MI is much less than 10% (in some studies 1–2.6%).
- An abnormal ECG can be seen in many non-cardiac conditions (pulmonary embolism, electrolyte abnormalities, aortic dissection).

Chest x-ray should be obtained on patients with chest pain.

- May show pneumothorax, pneumomediastinum (i.e., from esophageal rupture), pleural effusion, or infiltrates
- Aortic dissection can cause widening of the mediastinum
- Subtle findings such as loss of lung volume or unilateral decrease in vascular markings may suggest PE

Serum cardiac biomarkers also play a vital role in the evaluation of acute chest pain and the diagnosis of acute MI.

- **CK-MB isoenzyme** (typically measured upon ED admission and repeated 6–12 hours later)
  - Cardiac-specific; useful for early diagnosis of acute myocardial infarction
  - Typically detectable in serum 4–6 hours post-onset of ischemia, peaks in 12–24 hours and normalizes in 2–3 days
  - Peak CK-MB level can be useful for detecting early reinfarction since it normalizes 2–3 days post-initial MI (does not predict infarct size)
  - CK-MB subforms/isoforms (**not routine**): CK-MB1 is found in plasma, while CK-MB2 is found in myocardial tissue
- Cardiac troponins (**preferred markers**) (typically measured upon ED admission and repeated 6–12 hours later)
  - Troponins (T-I-C) are found in striated and cardiac muscle; because the cardiac and skeletal muscle isoforms of troponin T and I differ, they are known as the "cardiac troponins"

Note

Make every effort to obtain a previous ECG for comparison. Any ECG finding is assumed to be new unless proven otherwise by an old ECG (if one is available).

Note

Some markers are **no longer used in cardiac disease testing**, due to low specificity.

- Serum markers such as aspartate transaminase, lactate dehydrogenase, and lactate dehydrogenase subforms
- Total creatine kinase (CK), found in striated muscle and tissues of the brain, kidney, lung, and GI tract

  - Troponins T and I (**preferred in most settings**) have similar sensitivity for the detection of myocardial injury, but T (unlike I) may be elevated with renal disease, polymyositis, and dermatomyositis
  - Elevated T or I is helpful for identifying those at increased risk of death or of developing acute myocardial infarction. "Increased risk" relates to the high serum troponin level.
  - Troponins also can help identify those at low risk who may be sent home with close follow-up; those with a normal (or nearly normal) ECG and a normal troponin I test 6 hours post-admission have a very low risk of major cardiac events during the next 30 days
    - **Normal CK-MB and elevated troponin** = minor myocardial damage, or microinfarction
    - **Elevated CK-MB and elevated troponin** = acute myocardial infarction
  - May remain elevated up to 2 weeks after symptom onset, which makes them useful as late markers of recent acute MI
- **Myoglobin** begins to rise as early as 1–4 hours after the onset of pain. Normal myoglobin at 4 hours has a very high negative predictive value.

Especially if a noncardiac diagnosis is suspected, arterial blood gases, BNP, and CT angiogram may be helpful for evaluating acute chest pain.

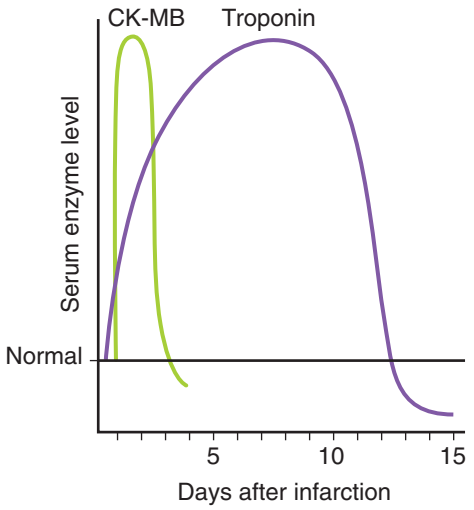


Figure 5-1. Progression of Cardiac Enzyme Serum Levels

Causes of Chest Pain

Aortic dissection. The pain is sharp/tearing/very severe; typically radiates to the back, and a loss of pulses or aortic insufficiency often develops.

- On chest x-ray, mediastinum is widened
- MI may occur if dissection extends into coronary artery
- Diagnosis confirmed by MRI, CT scan, or transesophageal echocardiogram

Pulmonary embolism. Dyspnea, tachycardia, and hypoxemia are prominent; pain is usually pleuritic, especially when pulmonary infarction develops.

- ECG is usually nonspecific but may show S wave in lead I, Q wave in lead III, or inverted T wave in lead III
- Diagnosis confirmed by CT angiogram

Pericarditis. May be preceded by viral illness; pain is sharp, positional, pleuritic, and relieved by leaning forward.

- Pericardial rub often present
- Diffuse ST elevation occurs without evolution of Q waves
- CK level usually normal
- Responds to anti-inflammatory agents

Table 5-1. Differential Diagnosis of Conditions Causing Chest Pain

Noncardiovascular Disorders	Differentiating Features
Costochondritis	Pain exacerbated with inspiration; reproduced with chest wall palpitation
Hiatal hernia	Reflux of food; relief with antacids
GERD	Acid reflux; relief with antacids
Peptic ulcer	Epigastric pain worse 3 h after eating
Gallbladder disease	Right upper quadrant abdominal pain and tenderness
Cardiovascular Disorders	**Differentiating Features**
Myocardial infarction	Pain more severe, usually >20 min in duration
Aortic stenosis	Typical systolic ejection murmur
Myocarditis	Pain is usually vague and mild if present
Pericarditis	Pain is sharper, pain worse with lying down and relieved by sitting up
Dissecting aortic aneurysm	Pain is sharp, tearing, often occurs in back
Mitral valve prolapse	Transient pain, midsystolic click murmur, and young female with no risk factors
Pulmonary Disorders	**Differentiating Features**
Pulmonary embolus-infarction	Tachypnea, dyspnea, cough, pleuritic pain, hemoptysis, calf pain
Pulmonary hypertension	Signs of right ventricle (RV) failure
Pneumothorax	Sudden onset of pain and dyspnea

Myocarditis. May be preceded by viral illness; pain is generally vague and mild if present; total CK and MB fraction of CK (CK-MB) are often elevated; conduction abnormalities and Q waves may occur.

Musculoskeletal disorders. Most common cause of chest pain. Includes costochondritis, cervical osteoarthritis, radiculitis; pain is atypical, stabbing, localized, may be pleuritic; reproduced by motion or palpation; ECG changes absent.

GI disorders. Esophageal reflux is often made worse with recumbency or after meals; may be associated with regurgitation and relieved by antacids; episodes of spasm may be brought on by cold liquids, relieved by nitroglycerin, and may closely resemble angina or infarction; diagnosis may be confirmed by upper endoscopy or esophageal manometry. Peptic ulcer disease, pancreatitis, and cholecystitis may occasionally mimic infarction; abdominal tenderness is present, with radiation to back and elevated amylase in pancreatitis; sonography can confirm cholecystitis.

Pneumothorax. Onset abrupt with sharp pleuritic chest pain and dyspnea; breath sounds absent; chest x-ray confirms.

Pleuritis. Pain is sharp and increases on inspiration; friction rub or dullness may be present; other respiratory symptoms and underlying pulmonary infection usually present.

Clinical Recall

Which of the following is the single most important test in the management of chest pain?

A. CKMB
B. Troponin
C. Echocardiography
D. Electrocardiogram
E. Chest CT

Answer: D

ISCHEMIC HEART DISEASE

Ischemic heart disease (IHD) (or coronary heart disease) is an imbalance in coronary oxygen demand and supply resulting from insufficient blood flow. In nearly all cases, the reduction in blood flow is caused by coronary atherosclerotic disease.

When the atherosclerotic plaque ruptures, there is superimposed thrombus formation that acutely occludes the artery; this is the most common cause of life-threatening acute coronary syndromes.

Rarely, other abnormalities may occur (coronary artery embolism, coronary artery spasm, coronary arteritis, and coronary artery dissection) which may cause IHD in the absence of atheroma formation.

IHD is one of the most prevalent diseases in society, and those affected are likely to die from their disease. As part of a systemic process that involves all arteries in the body, it is an insidious process that begins in early adulthood with fatty streaks; these lesions progress into plaques and thrombus formation in middle age.

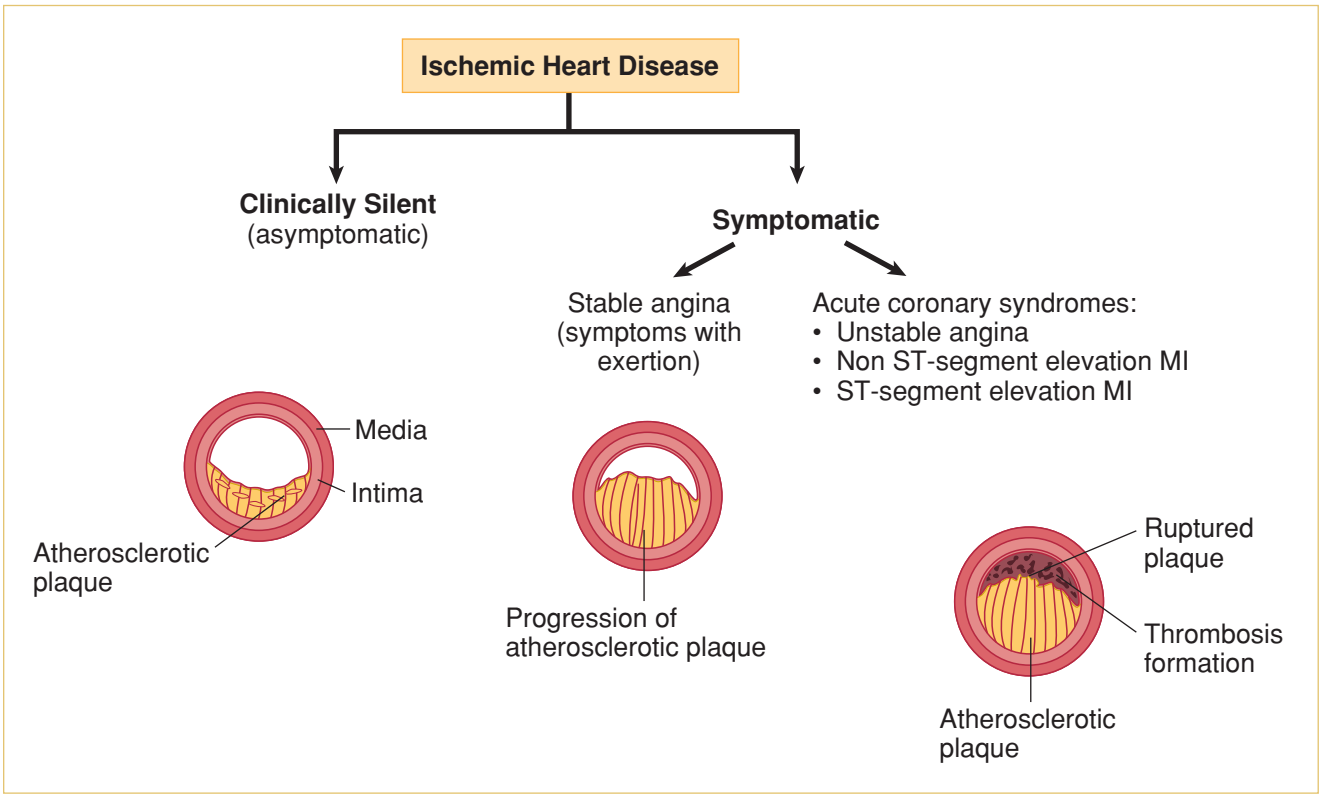


Figure 5-2. Ischemic Heart Disease

The more risk factors a person has, the greater the chance that he will develop heart disease. Also, the greater the level of each risk factor, the greater the risk. For example, a person with total cholesterol 260 mg/dL has a greater risk than someone with total cholesterol 220 mg/dL, even though all people with total cholesterol ≥220 mg/dL are considered high risk.

Major Modifiable Risk Factors

Some major risk factors for IHD can controlled with lifestyle change and medication.

- **Elevated cholesterol** (especially lipid fractions e.g., HDL and LDL)
  - LDL is most important subgroup but low HDL, hypertriglyceridemia, increased ratio of total-to-HDL, and increased lipoprotein A also increase risk
  - When other risk factors (such as high BP and tobacco smoke) are present, the risk increases even more
  - **High intensity statin** (high dose atorvastatin or rosuvastatin) should be given in the following situations:
    - Patient with clinical ASCVD (CAD, CVA, TIA, PAD, AAA)
    - LDL >190 mg/dL
    - Risk score >20%
  - For high-risk patients, **add ezetimibe** or a **PCSK9 inhibitor** (evolocumab or alirocumab) for additional LDL reduction.

Note

2013 AHA and 2016 USPSTF guidelines do not focus on LDL treatment targets, but rather on the overall risks of developing atherosclerotic cardiovascular disease.

The ASCVD 10-year risk score is based on risk factors and should be calculated. (On the exam, you will be provided with the value.)

Note

Proprotein convertase subtilisin/kexin type 9 (**PCSK9**) is an enzyme that binds to and degrades LDL receptors in the liver. PCSK9 inhibitors are monoclonal antibodies which reduce the degradation of LDL receptors and increase clearance of LDL cholesterol.

Note

In terms of **risk for IHD**, systolic BP is as important as diastolic BP, especially in older patients.

Note

- Almost 75% of patients with DM die of some form of cardiovascular disease.
- There is compelling evidence that aggressive treatment of HTN and cholesterol, as well as tight glycemic control, reduces the risk of cardiovascular events in these patients significantly.

  - **Moderate intensity statin** should be given in the following situations:
    - All patents age 40–75 with DM
    - All patients with ASCVD risk score ≥7.5%
  - Check baseline ALT; check CPK only if there are symptoms of myopathy
  - There is no need to monitor after starting therapy.

- **Tobacco**: A smoker's risk of heart attack is >2x that of a nonsmoker; cigarette smoking also acts with other risk factors (hypertension, dyslipidemia) to greatly increase the risk for IHD
  - Cigar or pipe smokers have a higher risk of death from IHD, though less than cigarette smokers.
  - Secondhand smoke or passive smoking increases the risk of heart disease, even for nonsmokers.
  - The risk for myocardial infarction in those who quit smoking is reduced to that of nonsmokers in 2 years, regardless of how much/how long the patient had smoked.
- **Hypertension** (HTN): HTN is a well-established risk factor for increased risk of myocardial ischemia, stroke, kidney failure, and heart failure. Studies in the general population have shown that the risk for cardiovascular events increases at BP >110/75 mm Hg.
  - Treatment of HTN to optimal levels reduces the risk of IHD and all cardiovascular events.
  - In fact, data from recent randomized trials suggest that reducing BP <130/80 mm Hg is beneficial in patients with cardiovascular disease and those with calculated 10-year cardiovascular risk >10%.
- **Physical inactivity and exercise**: Inactivity and sedentary lifestyle are risk factors for IHD. Even moderate exercise has a protective effect, and more vigorous exercise has added benefits. Specifically, exercise can increase HDL cholesterol, control diabetes/obesity, and lower blood pressure.
- **Obesity**: Increased body fat (elevated body mass index)—especially if concentrated in the waist area—increases one's risk for heart IHD and stroke. Excess weight raises BP, blood cholesterol, and triglyceride levels, and it lowers HDL cholesterol. It can also increase risk for type 2 diabetes by causing insulin resistance.
- **DM**: Elevated blood glucose and insulin resistance are associated with IHD and overall cardiovascular events. Even when glucose is under control, diabetes greatly increases the risk of IHD.

Major Non-modifiable Risk Factors

- **Age:** About 80% of people who die of IHD are age ≥65. Also, women who develop myocardial ischemia at an older age have a higher mortality than men within the first few weeks of the cardiac event.
- **Sex:** Men have a greater risk of IHD than women, and overall they develop cardiovascular disease earlier in life.
- **Heredity:** Family history is a significant independent risk factor if there is a family history of premature disease (age <55 in male relative and <65 in female relative).

Minor Contributing Risk Factors

- **Sex hormones**
  - Women before menopause have fewer heart attacks than men
  - Women after menopause have a higher risk of heart disease than men (studies show that the decrease of natural estrogen as women age may contribute to the higher risk)
- **Stress:** There is a proven relationship between IHD risk and stress, whether it is a true association or just a secondary correlation. For example, people under stress may overeat, start smoking, or be less active than people who are not under stress.

Myocardial Ischemia as a Manifestation of IHD

During ischemia, an imbalance occurs between myocardial oxygen supply and demand. Ischemia may manifest in any of the following ways:

- Anginal chest discomfort
- ST-segment deviation on ECG
- Reduced uptake of tracer during myocardial perfusion scanning
- Regional or global impairment of ventricular function

Myocardial ischemia can be caused by increased myocardial oxygen demand, reduced myocardial oxygen supply, or both. In the presence of coronary obstruction, an increase of myocardial oxygen requirements caused by exercise, tachycardia, or emotion leads to a transitory imbalance. (This condition is called **"demand ischemia"** and is responsible for most episodes of chronic stable angina.)

In other situations, the imbalance is caused by acute reduction of oxygen supply secondary to marked reduction or cessation of coronary flow as a result of platelet aggregates or thrombi. This condition (**"supply ischemia"**) is responsible for myocardial infarction (MI) and most episodes of unstable angina (UA). In many circumstances, ischemia results from both an increase in oxygen demand and a reduction in supply.

Angina (Stable Angina)

> A 62-year-old man presents with substernal chest pain that occurs with exertion and is relieved by rest, occurring on-and-off for 8 months. The last episode occurred 3 days ago while he was running to the bus. He has a history of well-controlled diabetes and dyslipidemia. Vital signs, physical examination, and ECG are normal. Exercise stress test shows a 2-mm ST depression.

Stable angina occurs when the myocardium becomes ischemic. This occurs during periods of increased demand for oxygen, such as exercise, or decreased supply, such as hypotension or anemia (see demand ischemia). Stable angina is typically a substernal pressure lasting 5–15 minutes. It may be accompanied by radiation to the jaw, neck, shoulders, or arms. It is less likely to have the symptoms often associated with MI: sweats, nausea, and shortness of breath. Anginal pain is not typically affected by respiration or by position. Typically, patients with stable angina will have pain after a predictable amount of exertion and will have identical symptoms with each attack.

Note

Studies have shown that weight loss of as little as 10–20 lb can significantly reduce the risk of cardiovascular disease.

Note

All-cause mortality in diabetic patients is comparable to that of all-cause mortality in patients with prior myocardial ischemia. Therefore, **diabetes is now considered an "IHD equivalent."**

In certain patients, symptoms other than pain may occur. For example, a profound sense of weakness and breathlessness may be an "angina equivalent." These symptoms are more likely to occur in women, the elderly, and diabetics.

The physical exam is usually normal. A new S4 may be heard, suggesting a stiff ventricle due to ischemia.

Most patients with angina will have ECG changes **during an attack**. Most commonly, ST segment depression is seen. ST segment elevation occurs in variant angina (Prinzmetal angina) where coronary artery spasm is responsible, and rarely during ischemia caused by stable angina (where atherosclerotic disease is responsible).

Note

The EST provides a controlled environment for observing the effects of increases in the myocardial demand for oxygen.

Diagnosis. The **exercise stress test** (EST) (treadmill test) is the most useful test for evaluating the cause of chronic chest pain when there is concern about IHD (stable angina).

To do an appropriate and accurate analysis, a target heart rate must be reached. Target heart rate is 85% of predicted maximum heart rate: **85% × (220 – patient's age)**.

Significant fixed stenoses (>50%) of the coronary arteries will result in ECG evidence of ischemia. Low-grade stenoses (<50%) may not produce sufficient impairment of blood flow to affect the ECG; in these cases the stress test will be normal.

An EST is considered positive for myocardial ischemia when large (>2 mm) ST-segment depressions or hypotension (a drop >10 mm Hg in systolic pressure) occur either alone or in combination. In general, the earlier the angina or ECG abnormalities occur, the more significant they will be. The exercise stress testing can help to do the following:

- Determine the severity of IHD and the need for further intervention, i.e., severe symptoms (hypotension) early in the test usually occur in those with triple-vessel disease
- Assess the effectiveness of treatment, i.e., CAD patients who have undergone surgical intervention or are receiving medical therapy have an exercise stress test when they are medically stable and symptom-free
- Determine functional capacity and identify any ECG changes or symptoms during (low level) exercise for patients who are post-MI

EST is contraindicated when it may place the patient at increased risk of cardiac instability, e.g., aortic dissection, acute myocardial infarction, unstable angina, or symptomatic supraventricular arrhythmia.

Patients who are unable to exercise or walk should be considered for **chemical stresstesting**, such as dipyridamole (Persantine) or dobutamine stress test. Presence of baseline ECG abnormalities such as bundle branch block, left ventricular hypertrophy, or with a pacemaker may make it more difficult to interpret test results. In those cases patients should be evaluated by nuclear stress imaging instead of the exercise stress test. These tests may also be used in patients who are taking digoxin.

For baseline LBBB or ventricular pacing, use a vasodilator stress radionuclide myocardial perfusion imaging, which has higher specificity. Exercise or dobutamine may result in a false-positive perfusion defect in the basilar septum.

In most cases, medications should not be withheld in preparation for an exercise stress test. Certain medications require special consideration:

- Beta blockers may blunt the heart rate during exercise and thus should be held 24 hours prior to the test. While patients receiving beta blockers may perform the exercise required for the test, the usual age-adjusted target heart rate may not be a realistic end point for them.
- Also, the antihypertensive effect of beta blockers, alpha blockers, and nitroglycerin may cause significant hypotension during exercise.

Digoxin may depress the ST segments, so if ST-segment depression of ≥1 mm is present on baseline ECG, the stress test results will be difficult to interpret.

A number of other situations or conditions may reduce the validity of the exercise stress test. Exercise testing in **asymptomatic young women** yields an increased number of false-positive results, while exercise testing in patients with known CAD may result in an unacceptably high false-negative rate (e.g., a negative stress test in a 64-year-old man with diabetes, hyperlipidemia, and typical stable angina is likely to be a false-negative result).

> A 29-year-old woman has a routine stress test done that shows a 1-mm ST depression. She has no history of chest pain, and she exercises routinely (runs 2–3 miles per day, 3 times per week). Her physical examination is unremarkable.

The most likely cause of this patient's abnormal stress test is a false-positive test.

Other types of stress tests include:

- **Nuclear stress test:** After injection of a radioactive substance, perfusion of heart tissue is visualized (perfusion pictures done both at rest and after exercise). An abnormal amount of thallium will be seen in those areas of the heart that have a decreased blood supply.
  - Higher sensitivity and specificity than regular stress test (92 and 95% versus 67 and 70%)
  - Not affected by baseline changes in ECG (LBBB, ST-segment depression at baseline, etc.)
- **Dobutamine or adenosine stress test:** used in those who are unable to exercise; a drug is given to induce tachycardia, as if the person were exercising
- **Stress echocardiogram:** combines a treadmill stress test and an echocardiogram; the latter can recognize abnormal movement of the walls of the left ventricle (wall motion abnormalities) that are induced by exercise

Invasive testing (angiography) is used when noninvasive tests are contraindicated or inadequate, or after a positive conventional stress test to identify whether patient will benefit from stent placement or bypass surgery.

Treatment.

- **Individual episodes of angina**: nitroglycerin (NTG) sublingual tablets (will alleviate pain within a few minutes)
- **Stable angina**: long-acting nitrates and/or beta blockers (nitrates must have a nitrate-free period of 8–12 hours (overnight) to prevent tachyphylaxis)

Note

Do not give adenosine if the patient is wheezing.

Note

High-yield points:

- Beta-blocker dose must be adjusted to achieve a resting HR of 60/min. Do not give if there is decompensated HF or active wheezing.
- Use verapamil or diltiazem if there is severe reactive airway disease.

Note

Almost all patients with chronic stable CAD will need statin therapy, unless contraindicated.

Note

CABG involves the construction of ≥1 grafts between the arterial and coronary circulations. (Many patients receive both arterial and venous grafts.) Long-term graft patency is significantly better with the arterial graph (e.g., internal mammary artery). Potential consequences of graft failure (loss of patency) include the development of angina, myocardial infarction, or cardiac death.

  - Lifestyle change, e.g., tobacco cessation, exercise, hypertension control
  - Unless contraindicated, add aspirin (reduces risk of stroke, MI, death) and high-intensity statins (for lipid lowering)
  - Evaluate severity of IHD (cardiac angiography or stress testing) and whether revascularization (stent or bypass surgery) would be helpful
  - Add ranolazine if no response with BBs, CCBs, and nitrites (monitor for QT prolongation)

Lipid lowering treatment for secondary prevention is important in IHD patients who should be treated aggressively. Most patients will require both pharmacologic and nonpharmacologic interventions. Target goals for hyperlipidemic patients with CAD include:

- LDL <100 mg/dL (<70 mg/dL if very high risk)
- HDL ≥40 mg/dL
- Triglycerides <150 mg/dL

Every effort should be made to ensure that patients with CAD receive optimal lipid therapy. **Statins** are strongly supported as first-line medications due to compelling evidence of mortality reduction. If patients are intolerant to a statin, consider other statins in reduced doses.

Better medical therapy with aspirin, beta blockers, ACE inhibitors, and statins are decreasing the need for all revascularization procedures.

Revascularization procedures include coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI).

- **Acute coronary syndrome**: PCI or CABG
- **Stable angina**: medical management first; if symptoms persist, consider PCI; for triple vessel and left-main disease, CABG has mortality benefit
- **Obstructive coronary artery disease**: CABG for the following patients:
  - Patients whose survival will be improved over medical therapy or PCI, e.g., patients with left main disease or triple-vessel disease and low ejection fraction
  - Patients with angina refractory to medical therapy
  - Diabetics

Clinical Recall

Which of the following is most likely to decrease a patient's risk for developing ischemic heart disease?

A. Tight glycemic control of patients with DM

B. Aggressive treatment of HTN

C. Aggressive treatment of hyperlipidemia

D. Smoking cessation

E. All of the above

Answer: E

ACUTE CORONARY SYNDROME

Acute coronary syndrome (ACS) describes a range of thrombotic coronary diseases including unstable angina (UA), non-ST elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI). Collectively they represent one of the most common causes of acute admission to U.S. hospitals.

ACS is caused by coronary vessel atherosclerotic obstruction with superimposed thrombotic occlusion. The natural course of coronary atherosclerotic plaque development and subsequent occlusion does not proceed in a step-wise, uniform manner, gradually progressing to luminal obstruction (and symptoms) over many years.

- The process is characterized by plaque disruption and mural thrombosis.
- Angiographic data support the concept that noncritical lesions account for the majority of the ACS.
- Thus, the pathogenic rate-limiting mechanism of the ACS appears to be acute thrombosis and the resultant obstruction of the coronary lumen.

An operational classification allows one to distinguish the types of ACS. In this classification, the ECG is the most important clinical tool. The initial ECG findings, in particular, the presence or absence of ST-segment elevation, will further define the patient's condition and dictate treatment options.

Note

- The term **ACS** is clinically useful because the initial presentation and early management of UA, STEMI, and NSTEMI are frequently similar.
- **Distinguish ACS from stable angina**, which develops during exertion and resolves at rest.

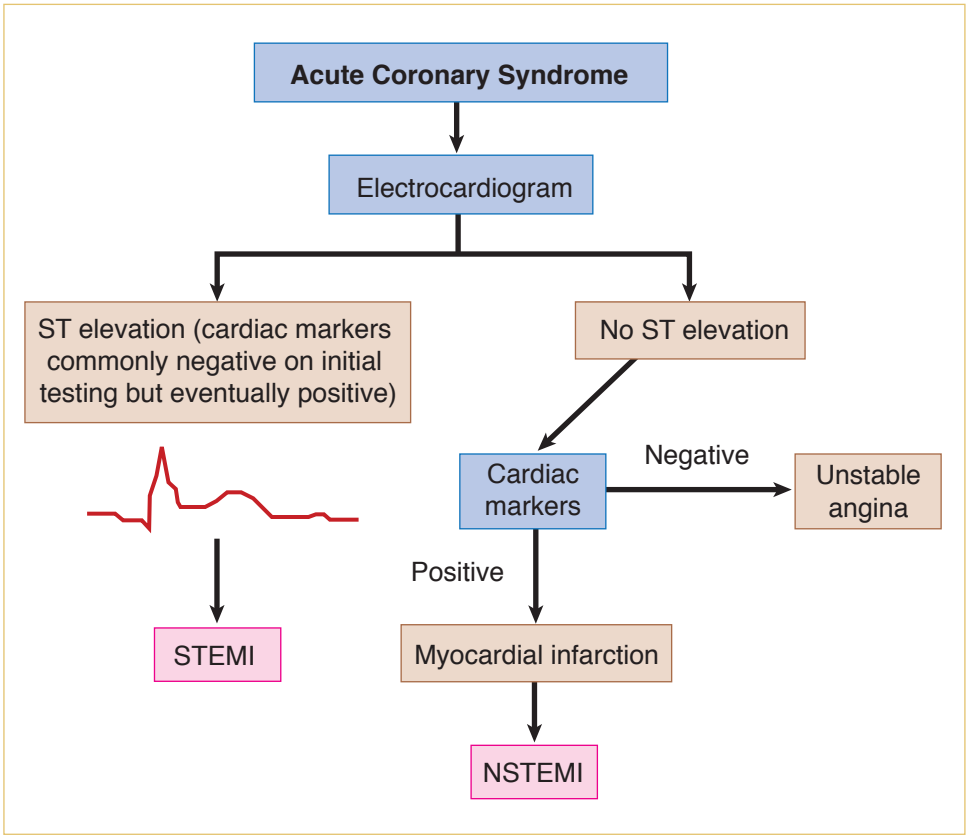


Figure 5-3. Acute Coronary Syndromes

UA and NSTEMI

UA and NSTEMI are closely related in terms of clinical presentation and pathogenesis, but patients with these conditions have widely varying risks. Both are usually caused by atherosclerotic CAD and present an increased risk for death and MI.

- At the time of presentation, UA and NSTEMI may be indistinguishable and can be identically managed. Use cardiac troponins to distinguish NSTEMI from UA (elevated enzymes show evidence of infarction).
- NSTEMI is more severe than UA and is considered to have occurred if ischemia produces damage detectable by biochemical markers of myocardial injury (troponin I or CK-MB).
- If there are no detectable serum markers of myocardial injury 12–18 hours after symptom onset, the diagnosis should be UA.

Outcomes in UA/NSTEMI are generally better than in STEMI, but certain UA/NSTEMI patients are at high risk for MI or death, and it is important to identify these patients at initial screening because they may require intensive monitoring and management.

Thrombolytic therapy is not effective in UA or NSTEMI and may be harmful, unlike the clear benefit in STEMI.

Sometimes referred to as "crescendo" or "preinfarction" angina, UA is defined as angina of increasing severity/frequency/duration, angina showing increased resistance to nitrates, or angina occurring at rest. Experts also regard **any new-onset angina** as unstable. Sudden change in the pattern of angina usually means a physical change within the coronary arteries, such as hemorrhage into an atherosclerotic plaque or rupture of a plaque with intermittent thrombus formation.

- About 35% of patients with the clinical syndrome of UA will already have coronary thrombosis on catheterization. In fact, untreated UA progresses to MI in 50% of cases. Thus, the patient with new-onset or UA should be hospitalized for intensive medical treatment.
- Most patients with NSTEMI have a normal physical examination. An abnormal ECG, particularly dynamic ST-segment deviation (≥0.5 mm) or new T-wave inversion (≥2 mm), will confirm the diagnosis, but the ECG may be normal or show minor changes in up to 50% of cases.

High-risk features for patients with presumed UA/NSTEMI include:

- Repetitive or prolonged chest pain (>10 min)
- Elevated cardiac biomarkers
- Persistent ECG changes of ST depression >0.5 mm or new T-wave inversion
- Hemodynamic instability (SBP <90)
- Sustained ventricular tachycardia
- Syncope
- LV ejection fraction <40%
- Prior angioplasty or prior CABG
- Diabetes
- Chronic kidney disease

Treatment.

- **Initial nonspecific management** in all cases of possible MI (anyone with a compatible chest pain history)
  - Cardiac monitor
  - Aspirin (unless contraindicated) as early as possible
  - Nitroglycerin and pain control (morphine) as needed
  - **High-risk patients**: aggressive medical management with coronary angiography and possible revascularization (unless contraindicated); age alone should not be a barrier to aggressive therapy
  - Antiplatelet therapy: clopidogrel, prasugrel, or ticagrelor (avoid clopidogrel if emergency coronary bypass surgery is likely to be required or at least discontinue 5 days beforehand)
  - Antithrombin therapy: unfractionated heparin, subcutaneous enoxaparin, or the bivalirudin (direct thrombin inhibitor) until angiography or for 48–72 hours
    - Reduce the enoxaparin dose for those with impaired renal function.
    - Give BB (unless contraindicated, i.e., severe asthma or cardiogenic shock).
  - Glycoprotein (GP) IIb/IIIa inhibitors to inhibit platelet function (block a key receptor involved in platelet aggregation)
    - Tirofiban or eptifibatide is recommended for high-risk patients in whom a PCI/stenting is planned (drug is given after PCI)
    - Concomitant tirofiban is recommended for patients with diabetes.
    - Side effects of all GP IIb/IIa agents include bleeding and thrombocytopenia (monitor patients closely for 24 hours)
  - IV nitroglycerin for refractory pain; initiate a high intensity statin immediately and an ACE inhibitor within 24 hours
- **Invasive management**
  - For patients with NSTEMI and high-risk features (unless contraindicated): early coronary angiography (within 24 hours) and revascularization
  - Pain or ischemia refractory to medical therapy and high-risk features on early exercise testing can also identify patients suitable for early invasive therapy.

For patients with diabetes, good glycemic control should be targeted in the hospital and after discharge. This may require considering an insulin-based regimen in hospital.

Note

Caution: Giving oxygen during an MI without hypoxemia has been shown to increase mortality.

Clinical Correlate

Glycoprotein (GP) IIb/IIIa inhibitors provide a more comprehensive platelet blockade than aspirin + heparin alone. These drugs take advantage of the fact that platelets play an important role in the development of ischemic complications, which may occur in those with UA/NSTEMI.

Clinical Recall

Which of the following medications must be withheld before an exercise stress test?

A. Clopidogrel
B. Metoprolol
C. Nimodipine
D. Aspirin
E. Lisinopril

Answer: B

Note

Patients with UA/NSTEMI do not benefit from thrombolytics.

Note

The strongest indication for PCI is an ACS.

STEMI

STEMI is defined as clinical symptoms consistent with ACS and ECG features, including any of the following:

- Persistent ST-segment elevation of ≥1 mm in 2 contiguous limb leads
- ST-segment elevation of ≥2 mm in 2 contiguous chest leads
- New LBBB pattern

Initially, increased cardiac biomarkers (troponin, CPK-MB, etc.) are not needed to make the diagnosis of typical MI (STEMI), although those are usually positive at some point during the course of the disease.

The pain that occurs with STEMI is substernal and diffuse, with a pressure quality. It may radiate to the neck or jaw, shoulders, or arms. Often, there are additional symptoms such as dizziness, nausea/vomiting, diaphoresis, or shortness of breath (dyspnea).

- Symptoms last >20 minutes and do not respond completely to nitroglycerin
- Duration of the pain is variable, i.e., may resolve in a few hours or may persist for more than 1 day
- Women, elderly, and diabetics are prone to atypical symptoms (e.g., nausea or dyspnea) as sole symptoms of infarction

As many as 20% of MI are "**silent**," i.e., whatever symptoms were present did not impress the patient enough to seek medical care or even to remember the incident.

- Exam usually shows patient to have anxiety and pain
- Diaphoresis often present
- Pulse may be normal, but there may be possible bradycardia (inferior infarctions) or tachycardia (large infarctions)
- Blood pressure often elevated
- Cardiac exam usually normal
- Signs of ventricular failure or valve dysfunction (large infarctions)
- Mitral regurgitation if papillary muscles malfunction

- Fourth heart sound (S4) (common) due to a stiffened ventricle
- Second heart sound may be paradoxically split as the left ventricular contraction time increases due to LBBB and weakened left ventricle

In advanced disease, mild fever, pericardial friction rub, ventral septal defect murmur due to septal rupture, or severe mitral regurgitation due to papillary muscle rupture may be seen.

Treatment.

Immediate treatment for STEMI is cardiac angiography. However, patients with STEMI usually have a completely occluded coronary artery with thrombus at the site of a ruptured plaque. This eventually leads to myonecrosis.

- Restoring coronary patency (emergency reperfusion) as promptly as possible is a key determinant of short-term and long-term outcomes.
- PCI (**preferred**) in <90 minutes of time of presentation (<120 minutes if transfer to another facility is required).
- If PCI not possible in required time interval, give thrombolytics.

Treatment for those with STEMI who present within 12 hours of the onset of ischemic symptoms is prompt reperfusion via fibrinolytic therapy or PCI.

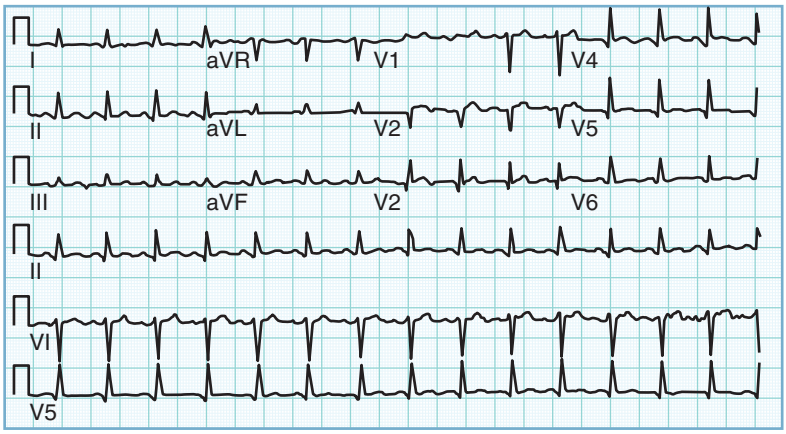


Figure 5-4. Anteroseptal STEMI with Changes in V_1–V_3

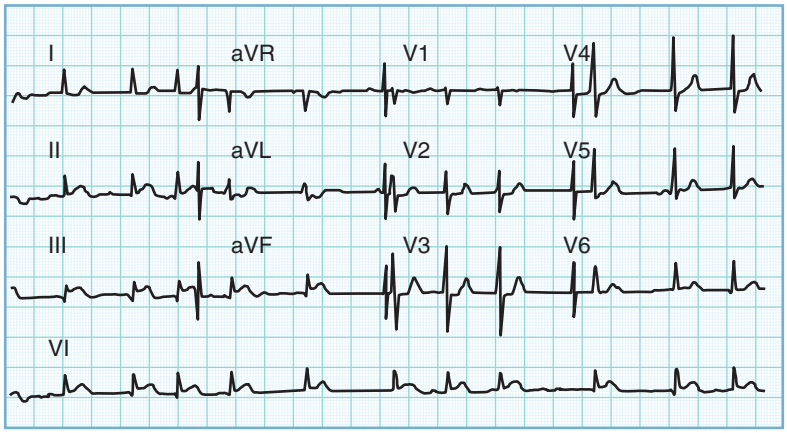


Figure 5-5. Inferior STEMI with Changes in II, III, and aVF

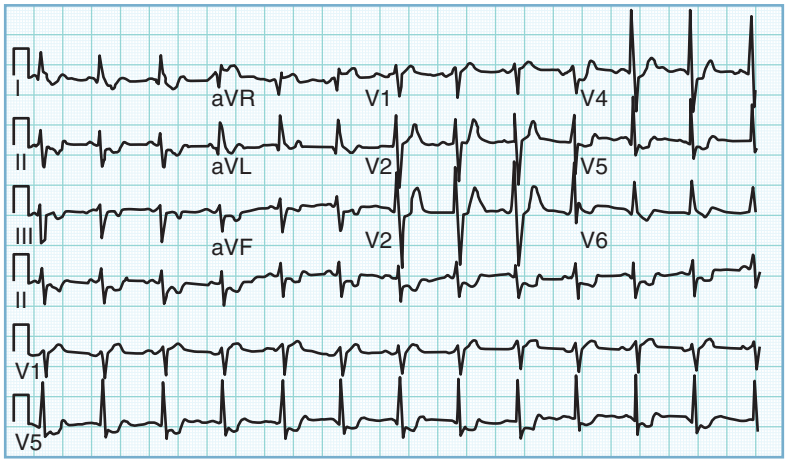


Figure 5-6. NSTEMI Affecting Leads II, III, and aVF

Table 5-2. Localization of STEMI

Area of Infarction	EKG Changes (Q Waves, ST Elevation, T Wave Inversions)	Artery Involved
Inferior	II, III, aVF	Right coronary
Anteroseptal	V_1–V_3	Left anterior descending
Anterior	V_2–V_4	Left anterior descending
Lateral	I, aVL, V_4, V_5, and V_6	Left anterior descending or circumflex
Posterior	V_1–V_2: tall broad initial R wave, ST depression, tall upright T wave; usually occurs in association with inferior or lateral MI	Posterior descending

Table 5-3. Typical Electrocardiographic Evolution of a STEMI

ECG Abnormality	Onset	Disappearance
Hyperacute T waves (tall, peaked T waves in leads facing infarction)	Immediately	6–24 hours
ST-segment elevation	Immediately	1–6 weeks
Q waves longer than 0.04 seconds	One to several days	Years to never
T wave inversion	6–24 hours	Months to years

Reperfusion therapy is with either PCI or thrombolysis therapy.

- PCI (**best option if provided promptly**)
  - Improves short- and long-term outcomes (reduction of deaths and MI) in patients with STEMI presenting within 12 hours, when compared with thrombolytic therapy
  - Benefit over thrombolysis is seen only if additional time delay associated with PCI is <1 hour; in general, a delay of 120 minutes from first medical encounter to PCI is the maximum desirable
  - Where PCI is delayed or not available, reperfusion with thrombolytic therapy should be used (unless contraindicated)
- Thrombolytics (fibrinolytics) such as streptokinase or tissue-type plasminogen activator (tPA) restore perfusion to the ischemic area by lysing the clot, thereby reducing infarct size and improving survival.
  - Can improve all types of ST elevation infarction, but has greatest benefit with anterior infarction
  - The earlier the treatment is given, the greater the absolute benefit (greatest benefit in patients who have had symptoms <12 hours)
    - tPA (**most common**)
    - Streptokinase and alteplase (IV infusion) (do not use streptokinase more than 1× in 12 months, as prolonged persistence of antibodies may reduce effectiveness of subsequent treatment)
    - Reteplase and tenecteplase (rapid bolus injection)

Thrombolytic therapy does have several contraindications.

- **Absolute contraindications**
  - Active bleeding or known bleeding diathesis
  - Significant closed head or facial trauma <1 month
  - Aortic dissection
  - Prior intracranial hemorrhage, tumor, or AVM
  - Ischemic stroke <3 months
  - GI bleed <1 month

Note

Consider thrombolytic therapy in candidates with ST-elevation MI (>1 mm ST elevation in 2 contiguous leads) or new LBBB.

- **Relative contraindications**
  - Recent major surgery (<3 weeks)
  - Pregnancy or <1 week post-partum
  - Traumatic or prolonged cardiopulmonary resuscitation
  - Active peptic ulcer
  - Severe, poorly controlled HTN (>180/110 mm Hg)
  - Advanced liver disease
  - Ischemic stroke (<3 months)
- **Late presentation (>12 hours after symptom onset):**
  - Reperfusion therapy with PCI or fibrinolysis is not routinely recommended in patients who are asymptomatic and hemodynamically stable, or in patients who present >12 hours after symptom onset.
  - Other interventions may include CABG, which may be appropriate for those who have suitable anatomy and are not candidates for fibrinolysis or PCI. CABG surgery may also be considered for those with cardiogenic shock or in association with mechanical repair.

Adjuvant therapy used together with reperfusion includes the following:

- **Antiplatelet therapy**
  - Aspirin should be given to all patients with presumed STEMI unless contraindicated, and, in the absence of significant side effects, low-dose therapy should be continued in the long term.
  - For patients undergoing PCI with a stent, add clopidogrel, prasugrel, or ticagrelor.
  - For patients selected for fibrinolytic therapy, add clopidogrel (however, if patient is likely to require CABG acutely, withhold clopidogrel).
  - Continue clopidogrel for at least 1 month after fibrinolytic therapy, or for 9–12 months after stent implantation (depending on type of stent used).
- **Antithrombin therapy**
  - **With PCI**: the dose of unfractionated heparin therapy will depend on concomitant use of GP IIb/IIIa inhibitors; it may be advisable to give a bolus of heparin while the patient is in transit to the catheterization laboratory; the role of enoxaparin in acute STEMI in conjunction with PCI is still unclear, but it appears to be safe and effective.
  - **With fibrinolysis:** use IV unfractionated heparin (shorter half-life) when rapid reversal is needed; give as an initial bolus, adjusted to attain APTT at 1.5–2× control
- **Glycoprotein IIb/IIIa inhibitors**
  - It is reasonable to use abciximab with primary PCI.
  - Eptifibatide and tirofiban are the other GPIIb/IIIa inhibitors.
  - Avoid full-dose GP IIb/IIIa inhibitors with fibrinolytic therapy, as that combination can cause excessive bleeding (including intracranial hemorrhage)

Emergency bypass surgery should be considered in patients with STEMI and one of the following conditions:

- Failed PCI with persistent pain or hemodynamic instability and coronary anatomy suitable for surgery
- Persistent or recurrent ischemia refractory to medical therapy and suitable anatomy

Discharge medications after ACS include the following:

- Aspirin, daily for all patients
- Clopidogrel (or prasugrel) for up to 12 months after acute myocardial infarction, particularly after stent placement; clopidogrel may also be used when aspirin is contraindicated, in patients with recurrent cardiac events
- BBs for all patients after an ACS, continued indefinitely (asthma is not a contraindication for BBs)
- Metoprolol or carvedilol for patients after ACS who have heart failure
- ACE inhibitors for patients who have CHF with left ventricular dysfunction (ejection fraction <40%); monitor and discontinue if the heart failure resolves
- Statins (for all patients with ACS, initiated when inpatient) (only exception is the rare ACS that is not related to atherosclerosis)
- Nitrates: long-acting nitrates (isosorbide) for patients with persistent chest pain
- Warfarin after ACS for those at high risk of systemic thromboembolism due to Afib or mural thrombus

Discharge planning should also include discussion of lifestyle modification, e.g., hyperglycemia in patients with DM, HTN control, tobacco cessation, and physical activity.

Note

To remember issues that need to be considered at the time of discharge, remember **"ABCDE"** (aspirin and antianginals, beta blockers and blood pressure, cholesterol and cigarettes, diet and diabetes, education and exercise).

Other testing in ACS

- **Exercise ECG testing:** submaximal testing is often performed 4–7 days after infarction; maximal testing can be performed at 3–6 weeks postinfarction. It is used to assess prognosis and to identify those patients with reversible ischemia who should then have an angiogram (if one has not been done) to assess the need for coronary artery bypass graft.
- **Myocardial perfusion imaging** can be performed before hospital discharge to assess the extent of residual ischemia if the patient has not already undergone cardiac catheterization and angiography.

Complications of ACS fall into cardiac and non-cardiac categories.

Cardiac Complications of ACS

- Electrical disturbances dysrhythmias
  - Bradycardia: sinus, atrioventricular junctional, idioventricular; treatment is atropine if acute and temporary pacing if severe
  - Premature beats: atrial, ventricular; no treatment is needed for ectopy such as these
  - Tachyarrhythmias (supraventricular): atrial tachycardia, Afib, atrial flutter, AV junctional; seldom caused by ischemia
  - Tachyarrhythmias (ventricular): ventricular tachycardia, accelerated idioventricular rhythm, ventricular fibrillation

- Conduction abnormalities
  - Atrioventricular nodal: first-, second-, and third-degree block
  - Intraventricular: hemiblocks (left anterior, left posterior), bundle branch block, third-degree atrioventricular block
- Pump dysfunction
  - Contractile dysfunction: left ventricular, right ventricular, and biventricular failure; true ventricular aneurysm; infarct expansion
  - Mechanical disruption: acute mitral regurgitation (papillary muscle dysfunction or rupture), ventricular septal rupture, free wall rupture, pseudoaneurysm; treatment is emergency surgical repair
  - Electromechanical dissociation
- Ischemia
  - Postinfarction ischemia: ischemia in the infarct and ischemia distant to the infarct
  - Early recurrent infarction or infarct extension
  - Postinfarction angina after thrombolytics or PCI; treatment is bypass surgery
- Pericarditis (Dressler syndrome)
  - Rare after PCI or CABG
  - Positional CP 2–4 weeks after MI
  - Treatment is aspirin and/or NSAIDs; if no response, try steroids
- Thromboembolic
  - Mural thrombus with systemic embolism
  - Deep vein thrombosis with prolonged immobilization
- Sudden cardiac death
  - Most often due to arrhythmia
  - Ventricular fibrillation (most common)
  - Ventricular tachycardia
- Right ventricular infarction (30% of inferior MIs): hypotension, JVD, clear lungs, ST elevated on V4R on right-sided ECG; treatment is fluids

Non-Cardiac Complications of ACS

- Depression (3× more common in heart attack patients than in general population): beyond the accompanying emotional distress, depression also increases one's risk of having another heart attack; treatment is antidepressant medication; psychotherapy; SSRIs such as sertraline and citalopram (safe with CAD); and cognitive behavioral therapy
- Erectile dysfunction (ED) (very common with CAD and post-MI)
  - ED is a complication of the conditions that are primary risk factors for developing CAD, e.g., diabetes, hypertension, dyslipidemias, and arteriosclerosis
  - Smoking and stress are implicated in the development of ED.

- Treatment is management of depression, reassurance, and modification of medications which may cause ED.
- Sildenafil is contraindicated in men post-MI who are taking nitrates up to 55 mm Hg, because it can cause a drop in BP.
- Although sexual activity can trigger MI, the relative risk is low with a slight increase in risk within 2 hours of sexual activity (applies equally to men and women)
- After MI, patients can be risk-stratified and counseled about safely returning to sexual activity:
  - **Low risk:** asymptomatic patients with <3 risk factors for CAD, stable angina, recent uncomplicated MI, mild valvular heart disease, mild CHF, controlled hypertension, or post successful revascularization; manage medically
  - **Intermediate risk:** those with recent MI (but >2 wks), moderate CHF (New York Heart Association class II), and those with >3 risk factors for CAD; patients may benefit from functional testing, i.e., EST, echocardiography, or nuclear imaging study with re-stratification. EST can assist in gauging cardiac risk of sexual activity, both for induction of ischemia or arrhythmia. In general, if a patient can achieve 5 METs on ETT without demonstrable ischemia or significant arrhythmia, he is not at high risk to resume normal sexual activities. Similarly, if echocardiography does not yield evidence of more than moderate left ventricular dysfunction, resumption of sexual activity is probably safe
  - **High-risk**: those with UA, MI within 2 weeks, poorly controlled hypertension, severe CHF (New York Heart Association class III/IV), significant arrhythmias, severe cardiomyopathies; patients have cardiovascular evaluation and stabilization before resumption of sexual activity

Nonatherosclerotic Acute Coronary Syndromes

Although thrombotic complications of the atherosclerotic process account for most cases of ACS, a few rare etiologic factors are likely causes of (or contributors to) acute coronary occlusion.

- Coronary artery spasm
- Spontaneous coronary dissection
- Coronary artery embolization
- Coronary arteritis
- Hypercoagulability states such as factor V gene mutation
- Deficiencies of proteins C and S
- Antithrombin III deficiency
- Antiphospholipid antibody syndrome
- Prothrombin gene mutation
- Cocaine use has been documented to induce coronary vasoconstriction in nondiseased coronary segments but is more pronounced in atherosclerotic segments.

Causes of MI without Coronary Atherosclerosis

- Vasculitis
  - SLE
  - Polyarteritis nodosa
  - Takayasu arteritis
  - Mucocutaneous lymph node syndrome (Kawasaki)
- Anomalous origin of coronary artery
- Coronary spasm
  - Variant angina
  - Cocaine abuse
- Coronary artery embolus
  - Atrial myxoma
  - Atrial or ventricular thrombus
- Hypercoagulable states
  - Polycythemia vera
  - Thrombocytosis
  - Factor V Leiden
  - Protein C deficiency
  - Antiphospholipid antibodies

Prinzmetal angina, or variant angina, is a rare condition in which episodes of severe angina are triggered when one of the major coronary arteries suddenly goes into spasm. The episodes are accompanied by ST-segment elevation on ECG. Although the spasm almost always stops spontaneously, Prinzmetal angina may be associated with acute MI, serious ventricular arrhythmias, and sudden death.

- Usually occurs during periods of rest, often at night and in the early morning (unlike typical angina)
- Episodes appear in clusters
- In men, associated with atherosclerosis
- In women, not associated with atherosclerosis but rather with a history of migraines (another condition associated with arterial spasm); also, women with Prinzmetal tend to have few risk factors for CAD

Exercise testing and routine coronary angiography usually give normal results. Ergonovine has been used to trigger coronary artery spasm in susceptible patients, confirming the diagnosis. Treatment with CCBs or nitrates eliminates spasm in most of these patients. Once adequately treated, their prognosis is good.

During an acute episode of pain and ST segment elevation, you cannot tell who has Prinzmetal variant angina and who has an acute ST elevation MI. Therefore, you must initially treat everyone with chest pain and ST elevation as if they were having an acute MI.

Prinzmetal angina can be confirmed only after coronary angiography.

Clinical Recall

Which of the following is not an absolute contraindication to thrombolytic therapy?

A. Active bleeding from factor VIII deficiency
B. Epidural hematoma within the last 3 months
C. Cholecystectomy 3 weeks ago
D. Prior basal ganglia hemorrhage
E. Large MCA stroke within the last 3 months

Answer: C

CONGESTIVE HEART FAILURE

Heart failure (HF) arises from the inability of the ventricle to efficiently pump blood throughout the circulation. Clinically, HF presents with symptoms of breathlessness, exercise intolerance, and fatigue.

Case 1:

A 62-year-old man with hypertension and dyslipidemia presents with dyspnea and lower-extremity edema for 2 months. On exam there is jugular venous distention (about 9 cm), an S3 gallop, and the apical impulse is displaced to the left of the mid-clavicular line at the 6th intercostal space. Chest x-ray shows enlarged cardiac silhouette. Echocardiogram shows a dilated left ventricle with ejection fraction 35%.

Case 2:

A 57-year-old man with history of multiple myeloma presents with dyspnea and lower-extremity edema for 2 months. On exam there is jugular venous distention (about 8 cm), an audible S4, and the apical impulse is non-displaced at the 5th intercostal space. Chest x-ray shows normal cardiac silhouette. Echocardiogram shows a thickened left ventricle with ejection fraction 65%.

As HF evolves, changes in vascular function, blood volume, and neurohumoral status occur throughout the body. These changes serve as compensatory mechanisms to help maintain cardiac output (primarily by the Frank-Starling mechanism) and arterial blood pressure (by systemic vasoconstriction). However, these compensatory changes over time can worsen cardiac function. Cardiac changes during HF include increased end-diastolic volume; ventricular dilatation or hypertrophy; decreased stroke volume and cardiac output; reduced

ejection fraction (systolic dysfunction) or impaired filling (diastolic dysfunction). Compensatory mechanisms during HF include:

- **Cardiac:** Frank-Starling mechanism, tachycardia, ventricular dilatation
- **Neuronal:** increased sympathetic adrenergic activity, reduced cardiac vagal activity
- **Hormonal:** activation of angiotensin-aldosterone system with renal sodium retention and ECV expansion), vasopressin, catecholamines, and natriuretic peptides

In clinical practice, HF is commonly categorized by whether the abnormality is due to contraction or relaxation of the heart.

- **Systolic HF** (systolic dysfunction) (also known as heart failure with reduced EF [HFrEF])
  - Caused by a loss of contractile strength of the myocardium accompanied by ventricular dilatation
  - Accompanied by a decrease in normal ventricular emptying (ejection fraction <45%)
  - Examples include ischemic and dilated cardiomyopathy (Case 1 in this section)
- **Heart failure with preserved ejection fraction** (diastolic dysfunction) (also known as heart failure with preserved EF [HFpEF])
  - Results when the filling of one or both ventricles is impaired while the emptying capacity is normal (ejection fraction >50%)
  - Examples include hypertensive heart disease and the infiltrative cardiomyopathies (amyloidosis) (Case 2 in this section)

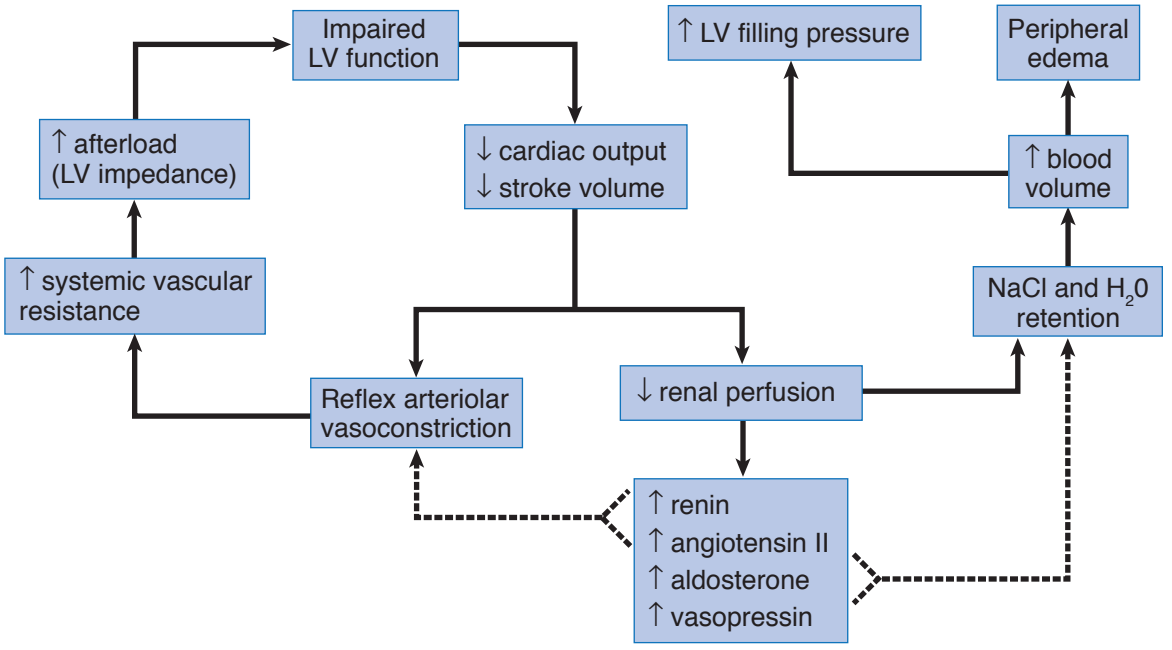
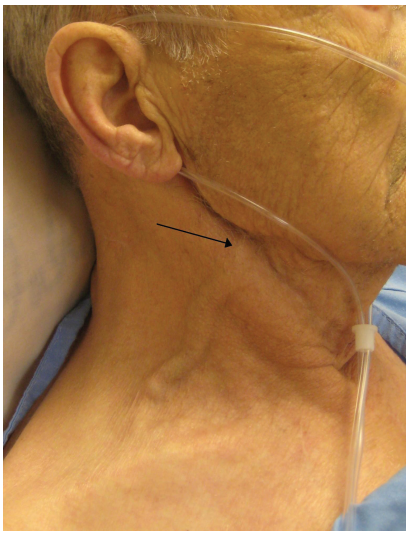


Figure 5-7. Inter-related Cycles in Congestive Heart Failure

Congestive HF indicates a clinical syndrome of dyspnea and fatigue as well as evidence of features of circulatory congestion (peripheral edema, elevated JVP). In heart failure, intravascular congestion occurs with elevation of left ventricular diastolic and pulmonary venous pressures that eventually causes transudation of fluid from the pulmonary capillaries into the interstitial space. The kidneys retain salt and water, worsening the EVC expansion. **Pulmonary edema** develops when the rate of fluid accumulation goes above the rate of lymphatic absorption. Pulmonary edema is detected by audible crackles, increased JVP and edema on exam, and chest x-ray findings.



Wikipedia, James Heilman, MD

Figure 5-8. Elevated JVP

Decompensated HF or exacerbation of HF denotes worsening of symptoms and clinical findings in pre-existing HF. This can be due to precipitating factors such as non-adherence to medication, increase in dietary salt, acute ischemia, tachycardia, or pulmonary infection.

In evaluating patients with HF or worsening of pre-existing HF, it is also important to exclude precipitating factors. Commonly, HF manifests for the first time when a precipitating factor places additional burden on the heart. Such factors include:

- Cardiac ischemia and myocardial infarction
- Infections (especially pulmonary infections)
- Arrhythmias (especially Afib)
- Excessive dietary salt (commonly after holiday meals)
- Uncontrolled hypertension (especially after abrupt cessation of anti-hypertensive medication)
- Thyrotoxicosis
- Anemia

HF may occur as a consequence of most causes of heart disease, but ischemic heart disease is responsible for over 70% of all cases in the western world. Other common causes include hypertensive heart disease, the cardiomyopathies (idiopathic, alcohol related, etc.), and valvular and congenital heart diseases.

Note

Both *hyper-* and *hypo*thyroidism can cause heart failure. Always check TSH with heart failure.

Clinical Pearl

In the work-up of patients with new-onset HF, always try to identify potentially reversible causes.

Clinical Presentation of CHF

Symptoms of HF include dyspnea (differentiate from pulmonary dyspnea), orthopnea, paroxysmal nocturnal dyspnea, and fatigue/weakness.

Clinical Pearl

In the work-up of patients with exacerbation of HF, always:

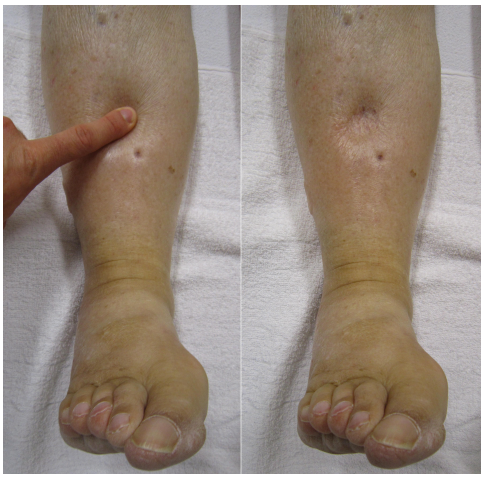
- Check cardiac enzymes to exclude myocardial ischemia or infarction
- Do a chest x-ray to exclude infection

Table 5-4. Most Common Causes of Acute Pulmonary Edema

Ischemia
Arrhythmia
Non-adherence with medication
Dietary indiscretion
Infection

Physical findings in HF:

- Pulmonary rales
- Peripheral edema, ascites
- Hepatomegaly
- Jugular venous distention
- Displaced apical impulse (systolic HF)



Wikipedia, James Heilman, MD

Figure 5-9. Pitting Edema

The severity of heart failure is commonly classified by using an HF staging system. The New York Heart Association Functional Classification (NYHA staging system) relates symptoms to everyday activities and the patient's quality of life:

- **Class I:** patients have no limitation of activity; they suffer no symptoms from ordinary activities
- **Class II:** patients with slight, mild limitation of activity; they are comfortable with rest or with mild exertion

- **Class III:** patients with marked limitation of activity; they are comfortable only at rest
- **Class IV:** patients are confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest

Diagnosis. An echocardiogram is the best test to confirm the diagnosis of HF and classify the type. With the echocardiogram, the clinician is able to determine ejection fraction and to identify valvular heart disease and other cardiac anomalies (dilated ventricle, thickened ventricle, etc.). Chest x-ray is also used the diagnosis of heart failure; it may show cardiomegaly, vascular redistribution, Kerley B-lines, or interstitial edema.

Electrocardiogram is used to identify ventricular hypertrophy and/or the presence of ischemic heart disease, arrhythmias, or conduction delays which may cause or precipitate HF.

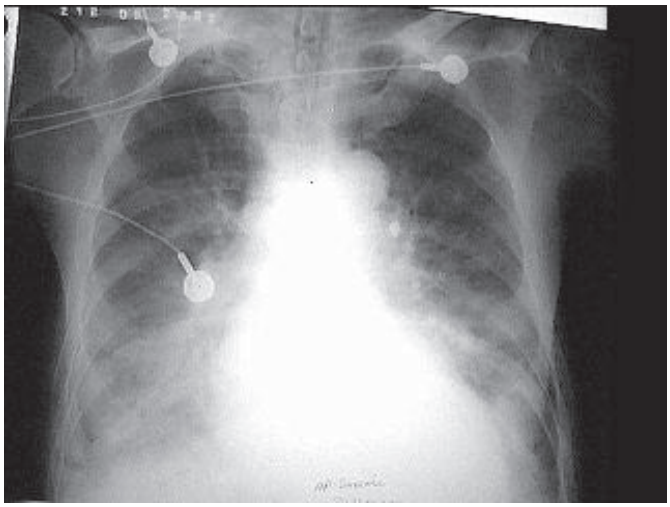


Figure 5-10. Chest X-ray Showing Acute Exacerbation of Congestive Heart Failure

Brain natriuretic peptide (BNP) (or type B natriuretic peptide) is a polypeptide secreted by the heart in response to excessive stretching of the myocytes. It is a valuable screening tool in the evaluation of presumed HF or decompensated HF in the acute setting.

- High sensitivity (97% sensitivity): almost always elevated in patients with decompensated HF (except obesity, where BNP can be falsely low)
- Low specificity (renal failure and old age can cause elevated BNP)
- Best used for ruling out HF
- Normal BNP generally excludes CHF as the cause of dyspnea
- Positive BNP warrants a follow-up echocardiogram.

Treatment. Treatment goals in HF are to improve hemodynamics, relieve symptoms (improve quality of life), and prolong survival. Always evaluate for reversible causes at the same time.

Note

Echocardiography is the best test to confirm CHF. **BNP** is best used to rule out CHF and save further workup.

Note

In terms of HF treatment, all ACE inhibitors are considered equal. If they are contraindicated, ARBs are an alternative.

- **Non-pharmacologic treatment**: reduction of salt intake
- **Pharmacologic treatment**
  - ACE inhibitors for all patients with HF, especially systolic HF, irrespective of BP status
    - Improve survival
    - Reduce ventricular hypertrophy (and eventually, symptoms)
    - Reduce preload and afterload (through vasodilation), thereby reducing right atrial, pulmonary arterial, and pulmonary capillary wedge pressures
    - Side effects include cough and angioedema
  - Newer drugs
    - Valsartan-sacubitril, an angiotensin receptor-neprilysin inhibitor (ARNI) (valsartan is an ARB, while sacubitril inhibits the degradation of natriuretic peptide); neprilysin is a neutral endopeptidase that degrades several vasoactive peptides, including natriuretic peptides (ANP, BNP) and bradykinin. Inhibition of neprilysin increases levels of these substances, which then counteract the effects of neurohormonal activation such as vasoconstriction and sodium retention. They block the RAAS system and lead to natriuresis and decrease cardiac hypertrophy and fibrosis.
    - Ivabradine, used for heart failure and tachycardia unresponsive to BBs, is an inhibitor of the If or "I-funny" channel, which contributes to normal sinus node function. Its sole effect is to slow the heart rate by decreasing sinus node automaticity.
  - Diuretics, especially loop diuretics, e.g., furosemide, to relieve symptoms of acute pulmonary edema (**treatment of choice**); thiazide diuretics (hydrochlorothiazide) are useful only in mild HF. Spironolactone and eplerenone (aldosterone antagonists) are used as add-on therapy to ACE inhibitors in severe HF to prolong survival by presumed aldosterone inhibition.
  - BBs play a role in helping to decrease mortality, reduce hospitalizations, improve functional class, and improve ejection fraction. Give a BB after patient is stabilized with diuretics and ACE inhibitor if BP is high. Metoprolol succinate, carvedilol, and bisoprolol are best shown to benefit mortality.
    - BBs are contraindicated in cardiogenic shock and severe active asthma.
    - BBs should never be given to someone with decompensated HF.
  - When ACE inhibitors/ARBs are contraindicated, another vasodilator such as combination hydralazine/isosorbide is helpful to reduce deaths and hospitalizations.
  - For severe HF or if no response to standard therapy, spironolactone may be helpful to reduce deaths and hospitalizations. Spironolactone is used in patients with NYHA class III-IV. Monitor serum potassium closely for possible hyperkalemia. Eplerenone is an alternative to spironolactone that does not cause gynecomastia.

Note

Hydralazine + nitrates is the best treatment for the following scenarios:

- African American patient with EF <40% and NYHA class III-IV while on standard therapy (do not pick this unless patient is on a BB and ACE inhibitor or ARB or NI/ARB and spironolactone)
- Patient cannot tolerate ACE inhibitors or ARBs

Monitoring of patients with HF includes calculation of fluid intake and excretion (inpatient) and monitoring of body weight (outpatient).

Table 5-5. Vasodilators Used in Congestive Heart Failure

Drug	Site of Action	Route of Administration	Complications
Captopril **Enalapril** **Lisinopril** **Sacubitril**	Arteriolar and venous ACE inhibitor	Oral	Rash, nonproductive cough, proteinuria, renal failure, taste disturbance, agranulocytosis, hypotension
Nitroprusside	Arteriolar and venous	IV	Thiocyanate toxicity, methemoglobinemia
Nitroglycerin	Venous (arteriolar at high doses IV)	SL, IV, cutaneous ointment, or patch	Headache, postural hypotension, methemoglobinemia
Isosorbide dinitrate	Venous	Oral or SL	Headache, postural hypotension
Hydralazine	Arteriolar	Oral	Positive ANA, SLE-like syndrome (10–20% if >400 mg/d) drug fever, rash

Table 5-6. Commonly Used Diuretics in Heart Failure

Drug	Site of Action	Complications
Thiazides (inhibits NaCl cotransport); used mostly for treatment of hypertension • Hydrochlorothiazide • Chlorothiazide	Distal tubule	Hyponatremia, hypokalemia, hypercalcemia, metabolic alkalosis, hyperuricemia, allergy, agranulocytosis, leukopenia, pancreatitis, glucose intolerance
Indapamide	Distal tube (direct vasodilator)	As above, but hypokalemia and lipid abnormalities less common
Loop diuretics (inhibitors Na/K, 2Cl cotransport); most commonly used diuretics in heart failure • Furosemide • Ethacrynic acid • Bumetanide	Loop of Henle	Hyponatremia, hypokalemia, hypocalcemia, metabolic alkalosis, hyperuricemia, interstitial nephritis, ototoxicity, thrombocytopenia, agranulocytosis, leukopenia
Potassium-sparing diuretics • Spironolactone (aldosterone antagonist)	Distal tubule	Hyperkalemia, gynecomastia (spironolactone only)

Note

Recent **guideline updates**, as per the American College of Cardiology/AHA, include the following:

- **ARNI** (not an ACEi or ARB) for patients with CHF and reduced ejection fraction (HFrEF) who are mildly/moderately symptomatic. Valsartan-sacubitril has been shown to lower risk for the composite endpoint of cardiovascular death or HF hospitalization compared with enalapril in patients with HFrEF. Do not administer valsartan-sacubitril concurrently, or within 36 hrs, of an ACEi, due to angioedema risk. Also, avoid in those with a history of angioedema.
- **Ivabradine** for reduction of heart failure-associated hospitalizations in patients with chronic symptomatic heart failure with left ventricular ejection fraction ≤35% if they are in sinus rhythm, taking guideline-directed medical therapy, and HR >70/min while on maximum dose of BB.

Note

ACEi (any) and a diuretic are considered first line for all patients with HF. Once the patient is stable, add carvedilol or metoprolol. Do not substitute BBs in HF since they are not all equally effective.

For **severe HF**, add an inotropic agent to improve quality of life and reduce hospitalizations (but will not improve survival). Digitalis (**most common**) inhibits Na^+/K^+-ATPase pump, which results in increased intracellular concentration of Na^+ and decreased exchanges of intracellular Ca^{2+}. The end result is improved cardiac contractility.

Note

Digitalis should be added only after all mortality-reducing drugs have been tried. Then it can be used for the treatment of systolic HF, Afib/flutter, and paroxysmal atrial tachycardia/SVT.

- Digitalis will increase both the force and the velocity of the myocardial contraction. It will also promote a more complete emptying of the ventricles.
- Monitor serum potassium in patients taking digitalis. Remember that K+ and digitalis compete for myocardium binding sites. Hyperkalemia will decrease digitalis action, while hypokalemia increases digitalis toxicity.
- Other conditions that predispose to digitalis toxicity are renal insufficiency; electrolyte disturbances (hypercalcemia, hypomagnesemia); advanced age; sinoatrial and atrioventricular block; and thyroid disease (especially hypothyroidism).
- Effects of digitalis toxicity include nausea and vomiting; gynecomastia; blurred vision; yellow halo around objects; arrhythmias (commonly paroxysmal atrial tachycardia) with block PVCs (premature ventricular contractions), and bradycardia. Treatment is to stop the drug and then add lidocaine and phenytoin (for arrhythmia). Digibind is used only for acute overdose.

Cardiac glycosides work by inhibition of Na+/K+-ATPase pump, which results in:

- Increased intracellular concentration of Na^+
- Decreased exchange of intracellular Ca^{2+} for extracellular Na^+
- The end result is an increase in the intracellular concentration of Ca^{2+}, which gives the (+) inotropic effect characteristic of glycosides

Table 5-7. Drug Interactions Associated with Digoxin

Drug	Effect*	Mechanism
Quinidine	Increase	Decreases renal clearance of digoxin
Verapamil, diltiazem	Increase	Decreases renal clearance of digoxin
Cholestyramine, colestipol	Decrease	Binds digoxin in GI tract; interferes with enterohepatic circulation
Spironolactone	Increase	Inhibits tubular secretion of digoxin
Thiazides, furosemide	Increase	Diuretic-induced hypokalemia and/or bumetanide hypomagnesemia potentiates digitalis action

*Increase enhances digitalis effect; decrease diminishes digitalis effect.

Note

ACE inhibitors/ARB, BBs, spironolactone, AICD, and biventricular pacing **all lower mortality** in systolic CHF.

Digitalis and diuretics do not reduce mortality but help in management.

Medical Devices for Systolic Dysfunction

After medical management has been initiated, several mechanical devices may be added to further improve prognosis in HF.

Note

Before either type of medical device is considered, the patient must have first tried 90 days of medical therapy.

- Automatic implantable cardioverter/defibrillator (AICD) is a standard therapy for severe ischemic dilated cardiomyopathy (EF <35%). Since the most common cause of death in CHF is an arrhythmia, it logical that a device which interrupts arrhythmia will lower mortality in patients with systolic CHF. Indications include ischemic or nonischemic dilated cardiomyopathy with persistent ejection fraction <35% and NYHA class II–III **or** ejection fraction <30% and NYHA class I on medical therapy.

- Biventricular pacemaker will "resynchronize" the heart when there is dilated cardiomyopathy. When there is a wide QRS, the 2 ventricles do not beat or depolarize in synchrony. The biventricular pacemaker will "resynchronize" the 2 ventricles, causing an immediate decrease in symptoms. This device also includes an automatic defibrillator, since patients are at risk for ventricular arrhythmia. Indications include dilated cardiomyopathy NYHA class II –IV, ejection fraction <35%, and LBBB with QRS >150 ms.

Treatment for dilated cardiomyopathy

The following classes of medications lower mortality in systolic HF:

- ACE inhibitor or ARBs (one or the other but not both); ARNI is better and should be used for class II or greater
- BBs (not all are equal; best mortality benefit is metoprolol succinate, carvedilol, or bisoprolol)
- Spironolactone (or eplerenone)
- AICD (if EF <35%)
- Biventricular pacemaker (LBBB with QRS >150 ms)

Treatment for Severe Systolic CHF

Additional support may be needed in hospitalized patients with cardiogenic shock. Patients are admitted to critical care units for support and treatment of hypotension and pulmonary edema. Fluid management is difficult, since increasing preload with fluids in an attempt to raise blood pressure may worsen pulmonary edema. In such hypotensive patients, BBs are now contraindicated, unlike outpatient CHF where they are first line.

Sympathomimetic inotropic amines (especially **dobutamine**) and phosphodiesterase inhibitors (amrinone, milrinone) are sometimes used to raise cardiac output in the management of severe acute systolic HF in hospitalized patients.

- Must be given by IV infusion
- Require continuous monitoring of BP and cardiac rhythm
- Do not use in renal failure
- Patients with ongoing infarction or ischemia are challenging, in that increasing the cardiac output also increases cardiac work and energy consumption, thus potentially extending the myocardial infarction.

In extreme HF with hypotension, the medications may fail, and the patient's heart may not be able to support circulatory function. In that case, an intra-aortic balloon pump can be used to improve perfusion and improve mortality. Extracorporeal membrane oxygenation (ECMO) may be used to remove the patient's RBCs, remove the CO_2 and supply O_2, then re-infuse into the patient. Biventricular assist devices (previously called "artificial hearts") may be used if the patient is awaiting heart transplantation. Heart transplantation is typically the only long-term effective treatment for very severe HF.

Pulmonary edema may occur in any patient with CHF, but is particularly likely in hospitalized patients with cardiogenic shock. It is considered a medical emergency and requires hospitalization. It leads to impaired gas exchange and may cause respiratory failure. There are non-cardiogenic causes of pulmonary edema, but in this section we will discuss only cardiogenic pulmonary edema. Cardiogenic pulmonary edema is caused by an acute increase in left

ventricular pressure due to ventricular dysfunction, which leads to fluid accumulation in the pulmonary interstitium.

Signs and Symptoms

- Tachypnea
- Cough with pink frothy sputum
- Cyanosis
- Pulmonary crackles or wheezes

Lab workup includes monitoring of blood oxygen and CO_2 content; chest x-ray (prominent pulmonary vessels, effusions, Kerley B lines); and ECG to exclude arrhythmias and ongoing MI.

Treatment in hospitalized patients includes all CHF treatments but also includes oxygen; IV loop diuretics (furosemide); morphine sulfate; nitroglycerin (reduces preload); IV ACE inhibitors; non-invasive positive-pressure ventilation in patients with severe hypoxia or hypercapnia after medications; and intubation/ventilation in patients who fail all of the above.

Management of Diastolic HF

Patients with diastolic HF (thick ventricles, preserved EF) do not benefit from inotropic agents, since their cardiac contractility is normal. ACE inhibitors are less useful than in systolic HF. Diuretics must be used cautiously, since limited preload (filling) is a hallmark of their disease.

Preferred management for HF with preserved systolic function includes the following:

- Diuresis as needed for volume overload
- BP control (CCBs, BBs, or ACE inhibitors/ARB)
- Exercise program and cardiac rehabilitation

BBs are now used less often but may be added for rate control of Afib or if patient has concurrent CAD.

Clinical Recall

What is the best therapy for hypertrophic cardiomyopathy?

A. Digoxin

B. Hydralazine/nitroglycerin

C. Lisinopril

D. Metoprolol

E. Nifedipine

Answer: D

VALVULAR HEART DISEASE

Mitral Stenosis

Mitral stenosis is the most common lesion caused by rheumatic fever, with possible progression to right ventricular failure. It becomes clinically symptomatic during pregnancy. Mitral stenosis consists of thickened mitral valve leaflets, fused commissures, and chordae tendineae.

Most cases are secondary to rheumatic fever. Rarely, it is caused by a congenital defect, calcification of the valve, or post-radiation treatment to the chest.

Pathogenesis. Mitral valve stenosis impedes left ventricular filling. Increased left atrial pressure is referred to the lungs, causing pulmonary congestion. Forward cardiac output becomes reduced, secondary pulmonary vasoconstriction occurs, and eventually right ventricular failure results.

Clinical Symptoms. Usually manifest slowly over years.

- Dyspnea
- Orthopnea
- Paroxysmal nocturnal dyspnea
- Fatigue
- Wasting
- Hemoptysis (due to rupture of pulmonary vessels)
- Systemic embolism (due to stagnation of blood in an enlarged left atrium)
- Hoarseness (due to impingement of an enlarged left atrium on the recurrent laryngeal nerve)
- Right-sided heart failure: hepatomegaly, ascites, peripheral edema

Physical Signs

- Afib (irregular cardiac rhythm)
- Pulmonary rales
- Decreased pulse pressure
- Loud S1
- Opening snap following S2
- Diastolic rumble (low-pitched apical murmur)
- Sternal lift (due to right ventricular enlargement)

Diagnosis is made with the following:

- **ECG**: possible signs of right ventricular hypertrophy; possible left and right atrial abnormalities; Afib (common)
- **Chest x-ray**: large left atrium (indicated by a double-density right heart border, posterior displacement of esophagus, and elevated left mainstem bronchus), straightening of left heart border; possible signs of pulmonary hypertension, including Kerley B lines and increased vascular markings; large pulmonary artery
- **Echocardiogram** (**best test**): thickening of mitral valve leaflets and a reduction in the excursion and area of the valve leaflets; possible left atrial enlargement; trans-esophageal echocardiogram often needed to visualize valve

Treatment.

- Medical therapy
  - Diuretics and salt-restricted diet
  - BBs or nondihydropyridine CCBs to control the ventricular rate in patients with Afib
  - Anticoagulants in patients with Afib
  - Balloon valvotomy (**standard of care**) (concurrent MR or left atrial thrombus is a contraindication to valvotomy); favorable characteristics include pliable leaflets, minimal commissural fusion, and minimal calcification
- Surgical management (repair) when patient remains functional class III-IV after medical therapy
  - Mitral commissurotomy or valve replacement when balloon valvotomy is contraindicated
  - Pulmonary hypertension is not a contraindication for surgery.

Note

All patients with Afib and MS should be on warfarin, regardless of CHA2DS2-vasc score.

DOACs cannot be used in MS.

Mitral Regurgitation

Mitral regurgitation is backflow of blood from the left ventricle into the left atrium due to inadequate functioning (insufficiency) of the mitral valve, most commonly from ischemia. Men > women.

The etiology of mitral regurgitation is due to abnormalities of the mitral leaflets, annulus, and chordae tendineae. Common causes include hypertension, CHF, ischemic heart disease, rheumatic fever, and any cause of dilation of the left ventricle.

Table 5-8. Acute versus Chronic Etiologies of Mitral Valve Regurgitation

Acute	Chronic
• Rupture chordae tendineae (permits prolapse of a portion of a mitral valve leaflet into the left atrium) • Papillary muscle rupture • Endocarditis (may lead to valvular destruction) • Trauma	• Rheumatic heart disease (causing scarring and retraction of valve and leaflets) • Papillary muscle dysfunction • Mitral valve prolapse (click-murmur syndrome, Barlow syndrome, floppy mitral valve) • Endocarditis • Calcification of the mitral valve annulus • Accompanying hypertrophic obstructive cardiomyopathy • Congenital endocardial cushion defect, corrected transposition • Endocardial fibroelastosis • Severe left ventricular dilatation

Pathogenesis

- A portion of the left ventricular stroke volume is pumped backward into the left atrium instead of forward into the aorta, resulting in increased left atrial pressure and decreased forward cardiac output. Traditional measurement of the cardiac output by EF may be normal, since the LV empties well. It is just not all in the correct direction. A regurgitant fraction needs to be estimated by Doppler during echocardiography.

- Volume overload occurs, increasing preload.
- Afterload is decreased as the left ventricle empties part of its contents into the relatively low-pressure left atrium.
- This helps to compensate for the regurgitation by augmenting ejection fraction.
- Left ventricular dysfunction occurs after prolonged compensation.

Clinical Manifestations

Left ventricular failure is manifested by dyspnea, orthopnea, and paroxysmal nocturnal dyspnea.

Severe and chronic mitral regurgitation lead to right-sided failure, presenting with edema, ascites, anorexia, and fatigue.

Pulmonary hypertension may be a late finding.

Physical Signs

- Hyperdynamic and displaced (downward and to the left) left ventricular impulse
- Carotid upstroke diminished in volume but brisk
- Holosystolic apical murmur radiating to the axilla and often accompanied by a thrill
- S3 heard with a soft S1 and widely split S2
- Distended neck veins when severe or acute

Diagnosis

- ECG shows signs of left ventricular hypertrophy and left atrial enlargement.
- Chest x-ray shows cardiac enlargement, with vascular congestion when the regurgitation has led to heart failure.
- Echocardiography (**best first test**): The mitral valve can prolapse into the left atrium during systole in cases of a ruptured chordae or mitral valve prolapse. Regardless of the cause, left atrial and left ventricular enlargement occurs if the condition is chronic.
- Left-heart catheterization is the single most accurate test.

Treatment

Medical therapy. The goal is to relieve symptoms by increasing forward cardiac output and reducing pulmonary venous hypertension. ARBs/hydralazine, arteriolar vasodilators (ACE inhibitors), digitalis, and diuretics are used.

Surgical therapy. Mitral valve replacement is indicated when symptoms persist.

- Indicated with significantly limiting symptoms and severe mitral regurgitation; the risk of surgery rises in chronic heart failure.
- Indicated when symptoms persist despite optimal medical management.
- Repair is preferable to replacement.

Patients with regurgitation but few symptoms should defer surgery, as their condition may remain stable for years.

Mitral Valve Prolapse

Mitral valve prolapse is the most common congenital valvular abnormality (2–3% population) typically seen in young women. It may occur with greater frequency in those with Ehlers-Danlos syndrome, polycystic kidney disease, and Marfan syndrome.

Most patients are asymptomatic. Lightheadedness, palpitations, syncope, and chest pain may occur (often due to arrhythmias, which may occur.)

Auscultation

- Mid-to-late systolic click and a late systolic murmur at the cardiac apex
- Worsens with Valsalva or standing
- Improves with squatting or leg raise

Complications (all very rare)

- Serious arrhythmias
- Sudden death
- CHF
- Bacterial endocarditis (but does not mean routine dental prophylaxis is indicated)
- Calcifications of valve
- Transient cerebral ischemic attacks

Lab tests include 2-dimensional/Doppler echocardiography showing marked systolic displacement of mitral leaflets with coaptation point at or on the left atrial side of the annulus; moderate systolic displacement of the leaflets with at least moderate mitral regurgitation.

Treatment. No specific treatment is needed in most cases. Use beta blockers for chest pain and palpitations. Mitral valve replacement is rarely needed.

Aortic Stenosis

Clinical Pearl

Look for AS in older patients presenting with syncope related to exertion.

Aortic stenosis is most commonly caused by calcification and degeneration of a congenitally normal valve. It is common in the elderly. Other etiologies include:

- Calcification and fibrosis of a congenitally bicuspid aortic valve
- Rheumatic valvular disease, i.e., if the aortic valve is affected by the rheumatic fever, the mitral valve is also invariably affected

Aortic stenosis results in elevation of left ventricular systolic pressure, and the resultant left ventricular hypertrophy maintains cardiac output without dilation of the ventricular cavity. Therefore, the stroke volume is normal until the late stages of the disease.

Forceful atrial contraction augments filling at the thick, noncompliant ventricle and generates a prominent S4 gallop that elevates the left ventricular end-diastolic pressure.

Left ventricular hypertrophy and high intramyocardial wall tension account for the increased oxygen demands and, along with decreased diastolic coronary blood flow, account for the occurrence of angina pectoris.

As the myocardium fails, mean left ventricular diastolic pressure increases, and symptoms of pulmonary congestion ensue.

Clinical Presentation.

- Angina, syncope, and dyspnea from CHF (classic symptoms)
- Pulsus tardus et parvus
- Carotid thrill

- Systolic ejection murmur in aortic area, usually with thrill, harsh quality, radiates to carotids
- S4 gallop
- A2 decreased, S2 single or paradoxically split
- Aortic ejection click

Diagnosis. ECG often shows left ventricular hypertrophy. Chest x-ray may present with calcification, cardiomegaly, and pulmonary congestion. Echocardiography shows thick aortic valve leaflets with decreased excursion and LVH.

Treatment. Endocarditis prophylaxis is no longer recommended.

- Surgery (valve replacement) is advised when symptoms develop, usually when the valve area is reduced <0.8 cm^2 (normal aortic orifice, 2.5–3 cm^2). Generally, if patient has symptoms, surgery is the treatment of choice.
- Balloon valvuloplasty may be useful in those too ill to tolerate surgery.

Table 5-9. Differential Diagnosis of Aortic Valve Stenosis

Disease Entity	Differentiating Features
Aortic valve sclerosis of the elderly, without stenosis	Systolic murmur does not peak late Carotids do not have delayed upstrokes No left ventricular hypertrophy by ECG Echocardiographic visualization of excursion of valve leaflets usually normal or mildly reduced, but valves may not be visualized No hemodynamically significant aortic valve gradient by cardiac catheterization
Hypertrophic obstructive cardiomyopathy	Brisk bifid carotid upstrokes Murmur usually does not radiate into neck Characteristic change in murmur with various maneuvers Pseudoinfarct pattern (large septal Q waves) on ECG Characteristic echocardiographic features
Mitral regurgitation	Murmur is holosystolic and radiates to axilla and not carotids Carotid upstroke may be normal Dilated left ventricle Aortic valve normal on echocardiogram unless there is associated aortic valve disease
Pulmonic stenosis	Murmur does not radiate into neck; loudest along the left sternal border; increases with inspiration Physical examination, chest x-ray, and ECG may reveal enlarged right ventricle Echocardiogram reveals right ventricular enlargement and hypertrophy

Note: All of the above have a systolic murmur that can be confused with aortic stenosis.

Table 5-10. Effect of Various Maneuvers on Systolic Murmurs

	Valsalva	Phenylephrine Handgrip	Squatting	Amyl Nitrite	Leg Raising
Aortic stenosis	Decrease	Decrease	Increase or decrease	Increase	Increase
Hypertrophic obstructive cardiomyopathy	Increase	Decrease	Decrease	Increase	Decrease
Ventricular septal defect	Decrease	Increase	No change	Decrease	Increase
Mitral regurgitation	Decrease	Increase	Increase	Decrease	Increase

Aortic Regurgitation

The most common causes of aortic regurgitation are systemic hypertension and ischemic heart disease.

- May occur after infectious endocarditis
- May result from a condition which affects the ascending aorta: syphilis, ankylosing spondylitis, Marfan syndrome, rheumatic fever, aortic dissection, aortic trauma

Pathophysiology

Aortic regurgitation results in a volume overload of the left ventricle.

- The ventricle compensates by increasing its end-diastolic volume according to the Frank-Starling mechanism.
- The left ventricular dilation is thought to overstretch the myofibrils, leading to less actin–myosin interaction and decreased contractility.
- In acute severe aortic regurgitation, the left ventricle has not had the opportunity to dilate, its compliance is relatively high, and the aortic regurgitation therefore leads to very high left ventricular end-diastolic pressure.
- If mitral regurgitation ensues, the elevated left ventricular diastolic pressure is reflected back to the pulmonary vasculature, and acute pulmonary edema may occur.

Acute aortic regurgitation results in a lower cardiac output, narrower aortic pulse pressure, and a smaller left ventricle than does chronic aortic regurgitation.

Aortic diastolic pressure decreases in chronic aortic regurgitation because of both the regurgitation of blood into the left ventricle and a compensatory decrease in systemic vascular resistance to maintain forward cardiac flow to the periphery. The increased pulse pressure in chronic aortic regurgitation is due to the large stroke volume, causing increased systolic and decreased diastolic pressure.

Note

Remember, aortic regurgitation can cause 3 different murmurs.

Clinical Manifestations

- Dyspnea (most common complaint)
- Diastolic decrescendo murmur is the most typical.
- Systolic flow murmur

- Duroziez sign: systolic and/or diastolic thrill or murmur heard over the femoral arteries
- S3 in early left ventricular decompensation
- Austin-Flint murmur

Diagnosis

- **Echocardiography** (**best initial test**): dilated LV and aorta; left ventricular volume overload; fluttering of anterior mitral valve leaflet
- ECG: LV hypertrophy often with volume overload pattern (narrow deep Q waves in left precordial leads)
- Chest x-ray: LV and aortic dilation

Treatment. Endocarditis prophylaxis is no longer recommended.

- Salt restriction, diuretics, afterload reduction (e.g., ACE inhibitors)
- Aortic valve replacement when symptoms worsen or ejection fraction decreases.
- Vasodilators such as an ACE, ARB, or nifedipine are the standard of care.
- Perform aortic valve replacement when the ejection fraction is <50% with HF symptoms (NYHA level II-IV) or left ventricular systolic diameter is >55 mm.

Clinical Recall

Which of the following is most appropriate in the management of a patient with aortic stenosis?

A. Warfarin to patients who develop atrial fibrillation

B. Surgical replacement when the EF <60% or LV end systolic diameter >40 mm

C. Surgical replacement when the valve area <0.8 cm^2

D. Surgical replacement when the EF <55% or LV systolic diameter >55 mm

E. None of the above

Answer: C

CARDIOMYOPATHIES

Cardiomyopathy is a disease involving the heart muscle itself. Cardiomyopathies can be classified according to morphologic and hemodynamic characteristics.

Table 5-11. Morphologic and Hemodynamic Characteristics of Cardiomyopathies

	Dilated	Hypertrophic	Restrictive
	Biventricular dilatation	Marked hypertrophy of left ventricle and occasionally of right ventricle; can have disproportionate hypertrophy of septum	Reduced ventricular compliance; usually caused by infiltration of myocardium (e.g., by amyloid, hemosiderin, or glycogen deposits)
Cardiac output	↓	Normal or ↓	Normal to ↓
Stroke volume	↓	Normal or ↑	Normal or ↓
Ventricular filling pressure	↑	Normal or ↑	↑
Chamber size	↑	Normal or ↓	Normal or ↑
Ejection fraction	↓	↑	Normal to ↓
Diastolic compliance	Normal	↓	↓
Other findings	May have associated functional mitral or tricuspid regurgitation.	Obstruction may develop between interventricular septum and septal leaflet of mitral valve.	Characteristic ventricular pressure tracing that resembles those recorded in constrictive pericarditis, with early diastolic dip-and-plateau configuration

Dilated (Congestive) Cardiomyopathy

Characterized by diminished myocardial contractility, usually involving both ventricles; most common cause for heart transplants.

Etiologies include:

- Ischemic (**most common**)
- Idiopathic (**next most common**)
- Alcoholic
- Peripartum
- Postmyocarditis due to infectious agents (viral, parasitic, mycobacterial, *Rickettsiae*)
- Toxins (cobalt, lead, arsenic)

- Doxorubicin hydrochloride, cyclophosphamide, vincristine
- Metabolic: chronic hypophosphatemia, hypokalemia, hypocalcemia, uremia

Clinical Manifestations. Symptoms and signs of left and right ventricular failure. Typical symptoms of systolic dysfunction.

Diagnosis

- X-ray: cardiomegaly with pulmonary congestion
- ECG: sinus tachycardia, arrhythmias, conduction disturbances
- Echo (key diagnostic study): dilated left ventricle, generalized decreased wall motion, mitral valve regurgitation; transesophageal echo is more sensitive and specific than transthoracic
- Catheterization: dilated hypocontractile ventricle, mitral regurgitation

Treatment is the same as those with systolic heart failure. ACE, BBs, and spironolactone lower mortality. Diuretics and digoxin decrease symptoms. Implantable defibrillator may decrease risk of sudden death when ejection fraction <35%.

Hypertrophic Cardiomyopathy

These disorders with thickened ventricles present with diastolic dysfunction.

- Hypertensive cardiomyopathy (from years of untreated hypertension, similar to hypertensive nephrosclerosis in the kidney)
- Hypertrophic obstructive cardiomyopathy (HOCM)

Hypertrophic Obstructive Cardiomyopathy

Although hypertrophic obstructive cardiomyopathy (HOCM) can apparently develop sporadically, it is hereditary in >60% of cases and is transmitted as an autosomal dominant trait.

- An abnormality on chromosome 14 has been identified in the familial form of the disease.
- The distinctive hallmark of the disease is unexplained myocardial hypertrophy, usually with asymmetric thickening of the **interventricular septum**.

Pathophysiology. As a result of the hypertrophy, left ventricular compliance is reduced, but systolic performance is not depressed. Diastolic dysfunction is characteristic, resulting in decreased compliance and/or inability for the heart to relax.

- The heart is hypercontractile, and systole occurs with striking rapidity.
- Ejection fractions are often 80–90% (normal is 60%, ±5%), and the left ventricle may be virtually obliterated in systole.
- An aberrantly protruding mitral valve with long leaflets may obstruct LV outflow (the obstructive component of HOCM).
- Obstruction is influenced by several factors.

Table 5-12. Factors That Modify Obstruction in Hypertrophic Obstructive Cardiomyopathy

Increase Obstruction		Decrease Obstruction	
Mechanism	**Physiologic or Pharmacologic Factors**	**Mechanism**	**Physiologic or Pharmacologic Factors**
Increase in contractility	Tachycardia Digitalis glycosides β-adrenergic stimulation (e.g., epinephrine, exercise) Premature beats	Decrease in contractility	β-adrenergic blockade Heavy sedation and general anesthesia Calcium channel blockers, disopyramide, and other drugs that depress myocardial function
Reduction in preload	Valsalva maneuver Decrease in intravascular volume Standing Nitroglycerin Vasodilator drugs Tachycardia	Increase in preload	Intravascular volume expansion Squatting Bradycardia β-adrenergic blockade
Reduction in afterload	Hypovolemia (diuretics) Nitroglycerin and related drugs Vasodilator drugs	Increase in afterload	Intravascular volume expansion Squatting α-adrenergic stimulation (e.g., phenylephrine) Handgrip

Clinical Manifestations

- Dyspnea, angina, presyncope, syncope with exertion, and palpitations
- Large jugular A wave, bifid carotid pulse, palpable S4 gallop, systolic murmur and thrill, mitral regurgitation murmur
- Sudden death can sometimes be the first manifestation.

Diagnosis

- ECG: left ventricular hypertrophy, pseudo Q waves (often seen V_1–V_3), ventricular arrhythmias
- **Echocardiogram** is the mainstay of diagnosis. It typically shows hypertrophy, systolic anterior motion of mitral valve, and midsystolic closure of aortic valve.

Treatment

- Beta-blockers
- Calcium channel blockers that reduce heart rate: diltiazem, verapamil
- Disopyramide, occasionally
- Use implantable defibrillator if there is syncope
- Surgery in severe cases—septoplasty

Restrictive Cardiomyopathy

Restrictive cardiomyopathy (least common cause of cardiomyopathy) is a myocardial disorder characterized by rigid noncompliant ventricular walls.

Etiologies are infiltrative (sarcoidosis/amyloidosis; hemochromatosis; neoplasia); scleroderma; and radiation.

Pathophysiology. The myocardium is rigid and noncompliant, impeding ventricular filling and raising cardiac filling pressures from abnormal diastolic function. Systolic performance is often reduced, but the overriding problem is impaired diastolic filling, which produces a clinical and hemodynamic picture that **mimics constrictive pericarditis**.

Clinical manifestations

- Dyspnea, exercise, intolerance, weakness
- Elevated jugular venous pressure, edema, hepatomegaly, ascites, S4 and S3 gallop, Kussmaul sign

Diagnosis

- X-ray: mild cardiomegaly, pulmonary congestion
- ECG: low voltage, conduction disturbances, Q waves
- Echo: characteristic myocardial texture in amyloidosis with thickening of all cardiac structures
- Catheterization: square root sign; elevated left- and right-sided filling pressures

Treatment. There is no good therapy; death ultimately results from CHF or arrhythmias. Consider heart transplantation.

Clinical Pearl

With HOCM, avoid the following:

- Digitalis
- Diuretics
- Vasodilators
- Exercise

PERICARDIAL DISEASE

Acute Pericarditis

Acute pericarditis is inflammation of the pericardial lining around the heart.

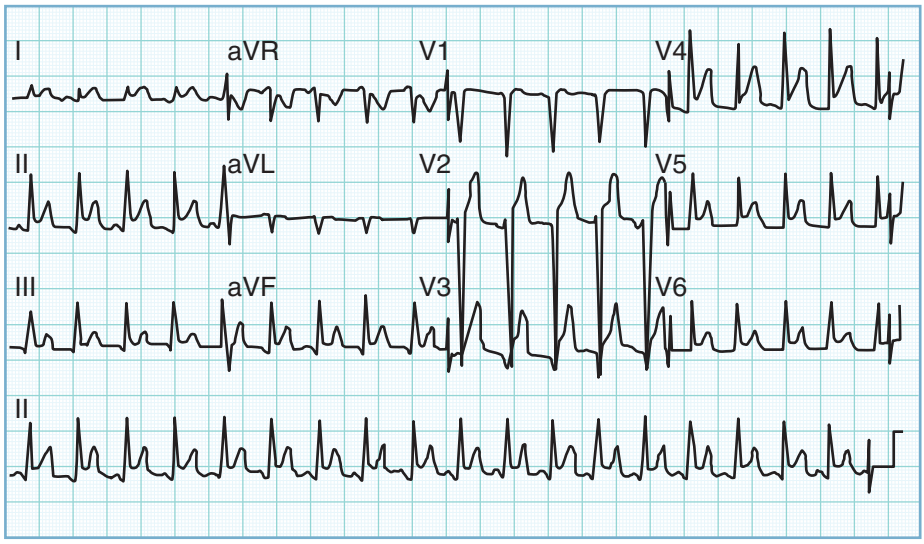


Figure 5-11. Acute Pericarditis with Diffuse ST Segment Elevation

Causes include:

- Idiopathic
- Infections (viral)
- Uremia
- Vasculitis (connective tissue diseases)
- Lupus (and other rheumatoid disorders)
- Disorders of metabolism
- Neoplasms
- Trauma

Clinical Manifestations. Chest pain, often localized substernally or to the left of the sternum, is usually worsened by lying down, coughing, and deep inspiration (which helps in the differential diagnosis with MI) and is relieved by sitting up and leaning forward.

Pericardial friction rub (diagnostic of pericarditis) is a scratchy, high-pitched sound that has 1 to 3 components corresponding to atrial systole, ventricular systole, and early diastolic ventricular filling. The ventricular systole component is present more consistently. The rub is often transient and is best heard with the diaphragm of the stethoscope as the patient sits forward at forced-end expiration.

Diagnosis.

- ECG reveals a diffuse ST-segment elevation with upright T waves at the onset of chest pain.
- PR segment depression is very specific.
- The diffuseness of the ST-segment elevation, absence of reciprocal leads, and absence of the development of Q waves **distinguish acute pericarditis** from **acute MI**.

Treatment is to treat the underlying cause. In idiopathic pericarditis, use NSAIDs, aspirin, and corticosteroids. Adding colchicine to an NSAID will decrease recurrence.

Pericardial Effusion

Fluid may accumulate in the pericardial cavity in virtually all forms of pericardial disease. The fluid may be a transudate, as in the serous cavity effusions that develop in patients with CHF, overhydration, or hypoproteinemia. More often, however, the pericardial effusion is an exudate, reflecting the presence of pericardial injury.

- Serosanguineous pericardial fluid is a classic sign in TB and neoplastic diseases.
- Frank blood in the pericardial space may occur in cases of aortic aneurysm or aortic dissection.
- Hemopericardium may also be produced by closed or penetrating trauma, rupture of the heart in acute MI, and bleeding caused by coagulation defects.
- When fluid accumulates slowly, the pericardium expands to accommodate it. When fluid accumulates rapidly, however, it compresses the heart and inhibits cardiac filling (cardiac tamponade).

Diagnosis. Echocardiography is the most effective laboratory technique available. The presence of pericardial fluid is recorded as a relatively echo-free space between the posterior pericardium and the posterior left ventricular epicardium in patients with small effusions. In patients with large effusions, the heart may swing freely within the pericardial sac, and this motion may be associated with electrical alternans.

Chest x-ray may show a "water-bottle" configuration of the cardiac silhouette.

Treatment. Treatment includes fluid aspiration and management of the etiology.

Cardiac tamponade

Cardiac tamponade is a life-threatening condition in which a pericardial effusion has developed so rapidly or has become so large that it compresses the heart. Symptoms include:

- Neoplasia
- Idiopathic (usually viral) pericarditis
- Nonviral infection: tuberculous; suppurative
- Intrapericardial hemorrhage with or without pericarditis
- Wounds, including surgery of chest; heart; pericardium
- Postpericardiotomy syndrome

- Uremia
- Mediastinal and juxtamediastinal radiation therapy
- Vasculitis–connective tissue disease group

Clinical Manifestations. Most patients with cardiac tamponade complain of dyspnea, fatigue, and orthopnea.

- Pulsus paradoxus, characterized by a decrease in systolic blood pressure >10 mm Hg with normal inspiration (very common)
  - The paradoxical pulse often can be noted by marked weakening or disappearance of a peripheral pulse during inspiration.
  - Paradoxical pulse is not diagnostic of cardiac tamponade; it can occur in chronic lung disease, acute asthma, severe CHF, and even hypovolemic shock.
- Neck vein distension with clear lung
- Shock (hypotension)
- Decreased heart sounds
- Beck's triad is associated with acute tamponade: low blood pressure, distended neck veins, and decreased heart sounds

Diagnosis. Clinical manifestations followed by echocardiogram. A surgical pericardial window may be needed for chronic effusions. Cardiac catheterization will confirm that left and right atrial pressures are equal.

Treatment is pericardiocentesis and subxiphoid surgical drainage.

Constrictive Pericarditis

Constrictive pericarditis is the diffuse thickening of the pericardium in response to prior inflammation, resulting in reduced distensibility of the cardiac chambers.

- Cardiac output is limited, and filling pressures are increased to match the external constrictive force placed on the heart by the pericardium.
- The fundamental hemodynamic abnormality is abnormal diastolic filling.

The disease is idiopathic, with an unknown etiology. Risk factors include open-heart surgery, thoracic radiation, and postviral infection.

Symptoms include:

- Dyspnea on exertion due to limited cardiac output (**common**)
- Orthopnea (50% of patients)
- Symptoms and signs related to systemic venous hypertension: ascites, edema, jaundice, hepatic tenderness, and hepatomegaly (manifestations of right-side failure)
- Jugular venous distension increased with inspiration (Kussmaul sign)
- Distant heart sounds
- Early diastolic apical sound ("pericardial knock") (**common**) can be confused with an S3 gallop

Diagnosis

- Chest CT or MRI (**best test**): thickened pericardium; pericardial calcifications may be seen in tuberculous constriction
- ECG: low-voltage and nonspecific T-wave changes
- Chest x-ray: heart is usually normal in size
- Cardiac catheterization
  - Marked "y" descent is present in right atrial pressure tracing
  - Characteristic "dip and plateau" or "square root" sign is present in left and right ventricular pressure tracing
  - Equalization of end-diastolic pressures in all 4 chambers and pulmonary artery

Treatment is conservative at first with mild sodium restriction and diuretics. Pericardiectomy may be needed.

Clinical Recall

Which of the following finding is most specific for the diagnosis of acute pericarditis?

A. Echocardiography showing ventricular wall thickening with a Kussmaul sign

B. Echocardiography showing echo-free space between the posterior pericardium and the posterior LV epicardium with distant muffled heart sounds

C. Cardiac catheterization showing a marked "y" descent in the right atrial pressure tracing with a Kussmaul sign

D. ECG showing a decrease in SBP >10 mm Hg with normal inspiration

E. ECG showing diffuse ST-segment elevation with PR segment depression

Answer: E

Peripheral Artery Disease

Risk factors include age, smoking, diabetes, and hyperlipidemia. Symptoms typically include intermittent claudication (cramping, tightness, aching of buttock, hip and lower extremities with exercise and improved with rest).

Diagnosis. Perform resting ankle-brachial index (ABI) (normal 0.9–1.40).

- ABI ≤0.9 is compatible with PAD.
- ABI ≤0.4 is associated with ischemic rest pain.
- When ABI >1.4, perform toe-brachial index; this is due to calcified, noncompressible arteries

Clinical Correlate

It can be difficult to distinguish **constrictive pericarditis** from **restrictive cardiomyopathy**. In the latter, left ventricular ejection fraction is more likely to be decreased.

Note

Toe-brachial index will provide a better assessment of the lower extremity perfusion.

CTA or MRA is performed in patients requiring surgical or endovascular intervention.

Treatment.

- Exercise training for all patients (**most effective treatment for improving functional status**)
- Goal BP <130/80 mm Hg
- Aspirin
- High intensity statin
- Cilostazol to improve pain and walking distance
- Angioplasty or surgery if no response to medical therapy, pain at rest, or poorly healing ulcers

Note

- Do not use cilostazol in low EF or history for CHF.
- Beta blockers are not contraindicated in PAD.

RATE AND RHYTHM DISTURBANCES

Sinus Bradycardia

Ventricular complexes are normal width, evenly spaced, rate <60/min.

- Excessive vagal tone causes: acute MI (particularly diaphragmatic); carotid sinus pressure; vomiting; Valsalva maneuver; phenothiazines; digitalis glycosides
- Depression of sinus node automaticity: beta-adrenergic blocking agents; calcium-blocking drugs
- Marathon running and swimming
- Hypothyroidism
- Normal variant

Treatment is atropine, but only if there are symptoms. For persistent symptoms and bradycardia, consider a pacemaker.

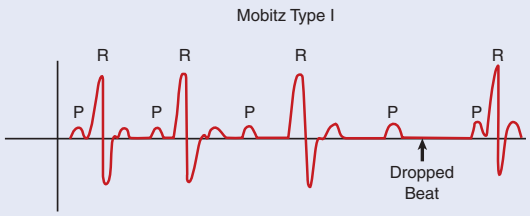
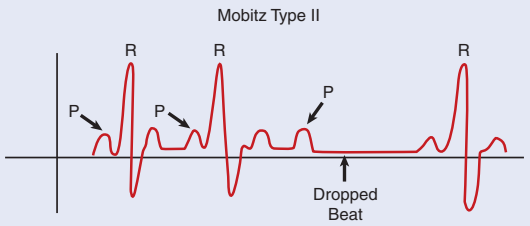
Atrioventricular Block

Atrioventricular (AV) block can be classified as **anatomical** (based on site of block as determined by His bundle electrocardiography), or as **clinical** (based on the routine ECG); classic types are first-, second-, and third-degree (or complete) AV block.

- **First-degree AV block** is pulse rate (PR) interval >0.20 s at heart rate 70 beats/min. It is caused by a cardiomyopathy or by a degenerative change in the AV conduction system due to aging, digitalis, exaggerated vagal tone, ischemia (diaphragmatic infarction), or inflammation (myocarditis, acute rheumatic fever). No treatment is needed.
- **Second-degree AV Block:** see table below
- **Third-degree (complete) AV block** is when all atrial beats are blocked, and the ventricles are driven by an escape focus distal to the site of block. The most common cause in adults is simple fibrous degenerative changes in the conduction system as a result of aging (Lenègre disease).

- Inferior or posterior infarction
- Infectious and inflammatory processes such as abscesses, tubercles, tumors, infiltrative disease of the myocardium, sarcoid nodules, gummas, myocarditis, and rheumatic fever
- Drugs like digitalis
- Ankylosing spondylitis

Table 5-13. Type I versus Type II Second-Degree AV Block

	Type I (Mobitz I, Wenckebach)	Type II (Mobitz II)
	 Progressive prolongation of the PR interval until a P wave is completely blocked and a ventricular beat is dropped. PR interval of the next conducted beat is shorter than preceding PR interval.	 Blocked beat occurs suddenly and is not preceded by a change in duration of the PR interval. Patient is equipped with a pacemaker, which cuts in to sustain a regular ventricular rhythm.
Site of block	Usually AV nodal (supra-Hisian)	Infranodal (intra- or infra-Hisian)
QRS complex	Usually normal in width	Usually wide (bundle branch block) with infra-Hisian block; narrow with intra-Hisian block
Causes	Degenerative changes in AV node; diaphragmatic myocardial infarct; digitalis toxicity; myocarditis; rheumatic fever; increased vagal tone	Extensive anterior myocardial infarct; degenerative changes in His-Purkinje system; massive calcification of mitral or aortic valve anulus
ECG	PR interval lengthens progressively until ventricular beat is dropped PR interval shortens after dropped beat RR interval lengthens progressively up to the dropped beat	PR interval is usually normal in duration and constant in length if PR interval is prolonged, the duration of prolongation is fixed Blocked beats occur suddenly without progressive lengthening of the PR interval RR interval of conducted beats is constant or a multiple of a basic RR interval cycle length
Effect of carotid sinus pressure	May increase degree of block	No effect
Effect of atropine	Frequently shortens PR interval and increases AV conduction	No effect
Consequences of progression to complete heart block	Escape focus usually junctional; narrow QRS complex; rate >45 beats/min; Adams-Stoke attacks uncommon	Escape focus infrajunctional (usually ventricular) wide QRS complex; rate <45 beats/min; Adams-Stoke attacks common. Junctional escape may be present with intra-Hisian block.
Treatment	None unless symptoms	Pacemaker

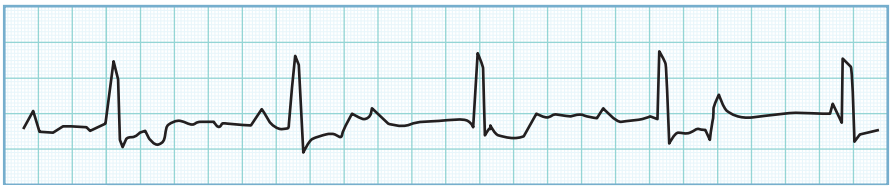


Figure 5-12. Third-Degree AV Block

Clinical Correlate

Adams-Stoke attacks are caused by sudden asystole or a ventricular tachyarrhythmia (transient ventricular tachycardia or ventricular fibrillation) and can lead to circulatory arrest.

Symptoms are associated with Adams-Stoke attacks and occasionally CHF. The bradycardia associated with complete heart block may lead to congestive heart block in patients with myocardial disease.

Treatment is pacing.

Supraventricular Arrhythmias

Sinus tachycardia is normal rhythm with rate >100/min. The ventricular complexes are of normal width, evenly spaced, and a P-wave precedes a QRS complex. It usually represents a physiologic response to fever, hypotension, volume depletion, anxiety, and pain. Other causes include thyrotoxicosis, anemia, and some drugs.

Transient sinus tachycardia is occasionally the result of a rebound phenomenon following the discontinuation of beta-adrenergic blocking drugs.

Treatment is of the underlying cause. Beta blockers are useful for symptoms.

Paroxysmal supraventricular tachycardia is a group of ectopic tachyarrhythmias characterized by sudden onset and abrupt termination. They are usually initiated by a supraventricular premature beat (includes paroxysmal atrial tachycardia). Eighty percent are caused by re-entry, mainly in the AV node. It manifests as an absolutely regular rhythm at a rate 130–220 beats/min (average 160).

Treatment.

- Carotid (particularly right carotid) sinus massage, which increases vagal tone
- IV adenosine (effective in >90% of cases) (do not give if patient is wheezing)
- Others: IV propranolol or esmolol, verapamil; IV digitalis
- Synchronized external cardioversion if patient is unstable

Multifocal atrial tachycardia is characterized by an irregular supraventricular rhythm, at 100–200/min.

- The morphology of the P waves (at least 3 different P wave forms) varies from beat to beat, as does the PR interval. Each QRS complex, however, is preceded by a P wave.
- Generally seen in elderly patients or those with chronic lung disease who are experiencing respiratory failure
- Use diltiazem, verapamil, or digoxin; avoid beta blockers because of lung disease

Atrial flutter generally presents as an absolutely regular rhythm with a ventricular rate 125–150/min and an atrial rate 250–300/min (i.e., 2:1 block). It has been associated with:

- Chronic obstructive lung disease
- Pulmonary embolism
- Thyrotoxicosis
- Mitral valve disease
- Alcohol
- Paroxysmal arrhythmia in persons with normal heart

Treatment is cardioversion if hemodynamically unstable (e.g., hypotension), digitalis, verapamil, diltiazem, and beta-blockers.

Unlike Afib, radiofrequency ablation is very successful and is preferred over medical therapy. Guidelines for anticoagulation are similar to Afib.

Atrial fibrillation (Afib) is the most common sustained cardiac rhythm disturbance. It is associated with heart disease but also occurs with no detectable disease. Thromboembolic events occur with Afib and can cause significant morbidity and mortality.

Afib is a supraventricular tachyarrhythmia characterized by uncoordinated atrial activation with subsequent decline of atrial function.

- On ECG, there is replacement of consistent P waves by fibrillatory waves that vary in size, shape, and timing, associated with an irregular, frequently rapid ventricular response (irregularly, irregular).
- The ventricular response to Afib depends on electrophysiologic properties of the AV node, the level of vagal and sympathetic tone, and the action of drugs.
- Extremely rapid rates (>200 bpm) suggest the presence of an accessory pathway (W-P-W syndrome), which may manifest as Afib.

When compared with atrial flutter, atrial flutter is found to be more organized than Afib, with a sawtooth pattern of regular atrial activation called flutter (f) waves on the ECG, particularly visible in leads II, III, and aVF.

The diagnosis of Afib should be considered in elderly patients who present with complaints of shortness of breath, dizziness, or palpitations. The arrhythmia should also be suspected in patients with acute fatigue or exacerbation of CHF. In some patients, Afib may be identified on the basis of an irregularly irregular pulse or ECG obtained for another condition.

Afib has both cardiac and noncardiac associations:

- **Cardiac conditions**: rheumatic mitral valve disease, CAD, CHF, and hypertension (cause atrial structures to dilate)
- **Noncardiac conditions**: hyperthyroidism, hypoxemia, and alcohol intoxication

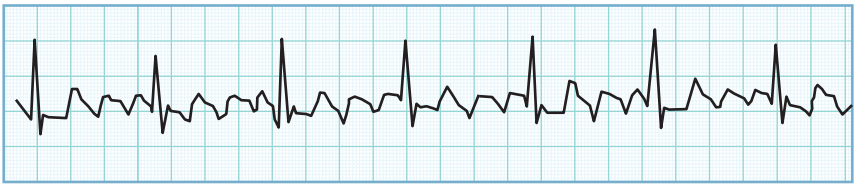


Figure 5-13. Atrial Flutter

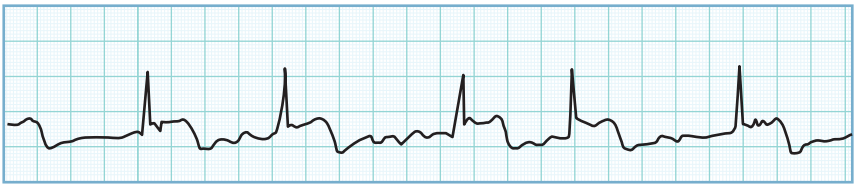


Figure 5-14. Atrial Fibrillation

Diagnosis of Afib begins with a minimum workup:

- **H and P:** identifies severity of symptoms associated with Afib, as well as the clinical type (paroxysmal, persistent, first episode); also allows assessment of frequency and duration of Afib, as well as identification of precipitating factors and presence of underlying heart or lung disease
- **ECG:** verifies the rhythm as well as identifies LVH, pre-excitation, prior MI
- **Chest x-ray:** allows evaluation of lung parenchyma and identifies coexisting lung disease
- **Echocardiogram:** identifies LVH, valvular disease, atrial size, and possible left atrial thrombus.
- **Thyroid function tests:** excludes hyperthyroidism as a cause of Afib

Treatment. The goals of initial management are hemodynamic stabilization, ventricular rate control, and prevention of embolic complications. When Afib does not terminate spontaneously, the ventricular rate should be treated to slow ventricular response and anticoagulation started.

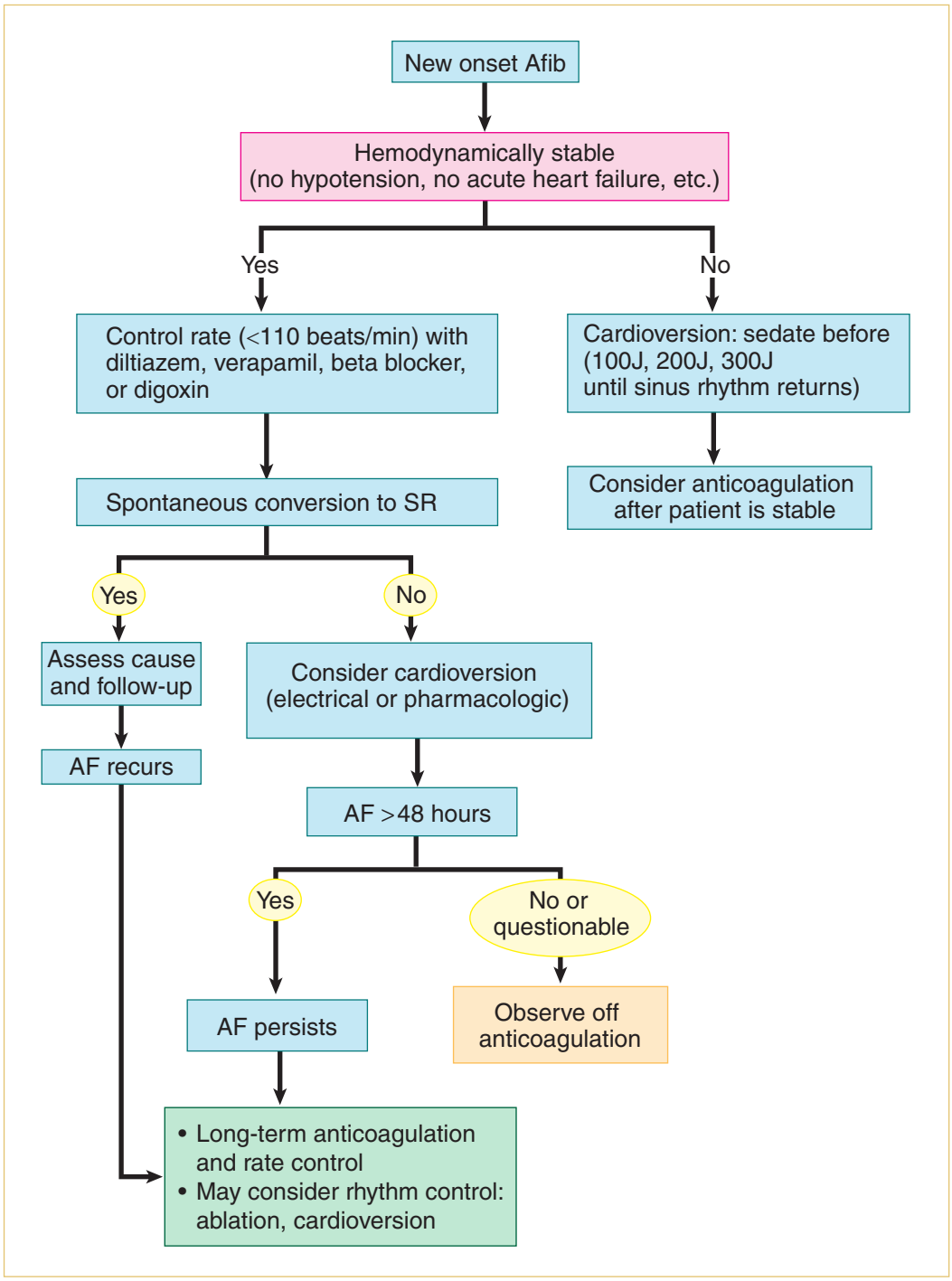


Figure 5-15. Management of Atrial Fibrillation

Note

There is little difference in outcome between rate control and pharmacologic rhythm control. Fewer than 25% of patients on an antiarrhythmic regimen remained in sinus rhythm at the end of 1 year.

Two approaches are used in management:

- Ventricular **rate control** (usually preferred) often considered for the patient who notices very few symptoms of the arrhythmia; initial goal <100–110/min but slower rates may be recommended for severely ill patients.
  - BBs, CCBs, and digoxin are most commonly used (note that they do not convert Afib to sinus rhythm and should not be used for that purpose); consider patient's condition and presence of concomitant heart failure when selecting a medication.
    - BBs and CCBs are effective at reducing the heart rate at rest and during exercise in patients with Afib.
    - Digoxin (because of the inotropic effects) is the drug of choice for patients with coexisting systolic heart failure.
  - Atenolol, metoprolol, verapamil, and diltiazem are effective in rate control at rest and during exercise.
- **Rhythm control** (attempts to convert to and maintain sinus rhythm) (for patients who are symptomatic on rate control, who immediately notice the arrhythmia and experience SOB, etc., or who develop heart failure)
  - **Mechanical cardioversion (more effective)** involves an electrical shock synchronized with the intrinsic activity of the heart. The synchronization ensures that electrical stimulation does not occur during the vulnerable phase of the cardiac cycle.
    - Performed electively to restore sinus rhythm in patients with persistent Afib
    - Performed for immediate need, i.e., when arrhythmia is main factor responsible for hemodynamic instability (acute heart failure, hypotension, or angina)
    - Carries a risk of thromboembolism, so when elective cardioversion, initiate anticoagulation beforehand
  - **Pharmacologic cardioversion** (with medications) is less effective than electrical cardioversion but does not require sedation or anesthesia, as does mechanical cardioversion.
- Carries a risk of thromboembolism, so initiate anticoagulation
- Drugs proven effective for Afib include amiodarone, dofetilide, flecainide, ibutilide, propafenone, and quinidine
- Drugs used to maintain sinus rhythm in patients with Afib include amiodarone, disopyramide, dofetilide, flecainide, propafenone, and sotalol

Note

Routine rhythm control for Afib is appropriate in younger patients with persistent symptoms.

Catheter ablation of Afib foci is a nonpharmacologic therapy for eradicating Afib, used when rhythm control is unsuccessful and patients are symptomatic. The procedure evolved from the understanding that most Afib is initiated by ectopic beats from focal areas that may be targeted for ablation. These foci arise more commonly from the 4 pulmonary veins. Techniques now focus identifying and eliminating these foci. After the procedure, patients must remain on anticoagulation.

Note

In patients with Afib and low EF, only amiodarone and dofetilide are safe options.

Anticoagulation. The rate of ischemic stroke among patients with nonrheumatic Afib averages 5% per year, which is 2–7× the rate for people without Afib. Therefore, anticoagulation is beneficial for many patients despite its risk of bleeding.

The CHA_2DS_2-VASc score is a clinical prediction rule for estimating the risk of stroke in a patient with Afib. It is used to determine whether anticoagulation or antiplatelet therapy is more appropriate. A high CHADS score corresponds to a greater risk of stroke.

- **C** for CHF
- **H** for hypertension
- **A** for age ≥75
- **D** for diabetes
- **S** for prior stroke or TIA

Assign 1 point each for CHF, HTN, age 65–74, DM, female sex, and vascular disease (previous, MI, PAD, aortic plaque). Assign 2 points each for CVA or TIA and age ≥75.

For score ≥1 (men) **and ≥2** (women), **give anticoagulation**.

- Dabigatran, rivaroxaban, or edoxaban is used for nonvalvular Afib.
- Warfarin is used for valvular Afib, i.e., the presence of a mechanical heart valve or mitral stenosis due to rheumatic heart disease.
- Heparin is not necessary before starting oral anticoagulants.

Anticoagulation is continued indefinitely.

Note

Control the heart rate, then anticoagulate.

Pre-excitation syndrome

Pre-excitation is a condition in which all or some portion of the ventricle is activated by atrial impulses earlier than if the impulses were to reach the ventricles by way of the normal cardiac conduction pathways. This is achieved by the use of accessory pathways (Kent bundle). **Wolff-Parkinson-White (WPW)** syndrome is the most common of these syndromes.

- ECG shows a short PR interval, followed by a wide QRS complex with a slurred initial deflection, or delta wave, representing early ventricular activation.
- WPW is associated with paroxysmal supraventricular arrhythmias alternating with ventricular arrhythmias, Afib, and atrial flutter.

Treatment is immediate synchronized cardioversion if the patient is hemodynamically **unstable**, and procainamide if the patient is hemodynamically **stable**. **Avoid digoxin, BBs, and CCBs**, as they can inhibit conduction in the normal conduction pathway, increasing aberrant conduction. That could increase the likelihood of developing ventricular or supraventricular tachycardia.

Ablation is used as definitive treatment.

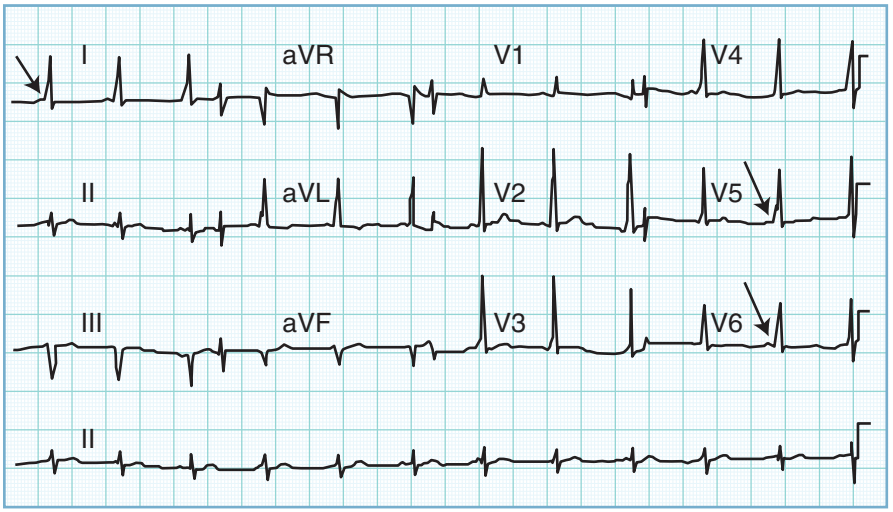


Figure 5-16. Wolff-Parkinson-White Syndrome

Ventricular arrhythmia

Ventricular tachycardia (VT) is ≥3 consecutive beats of ventricular origin at a rate >120 beats/min. QRS complexes are wide and often bizarre. Causes include:

- After an acute MI
- Cardiomyopathies
- Hypokalemia, hypercalcemia, hypomagnesemia, and hypoxia
- Digitalis toxicity
- Thioridazine drugs

Symptoms include concomitant hypotension, CHF, syncope, or cardiac arrest.

- Independent and asynchronous atrial and ventricular contractions produce the following signs. These signs are absent when Afib is present.
  - Variation in systolic BP, as measured peripherally
  - Variation in intensity of the heart sounds
  - Intermittent cannon A waves in jugular venous pulses caused by the simultaneous contraction of the atrium and ventricles
  - Extra heart sounds
- Because of asynchronous activation of the right and left ventricles, the first and second sounds are widely split.

Table 5-14. QRS Complex

Wide (>0.12 s)		Narrow (<0.12 s)	
Regular	**Irregular**	**Regular**	**Irregular**
Ventricular tachycardia	Afib (rarely)	Sinus tachycardia	Afib
Supraventricular tachycardia (aberration)		Paroxysmal supraventricular tachycardia	Multifocal atrial tachycardia
Wolff-Parkinson-White syndrome		Atrial flutter	

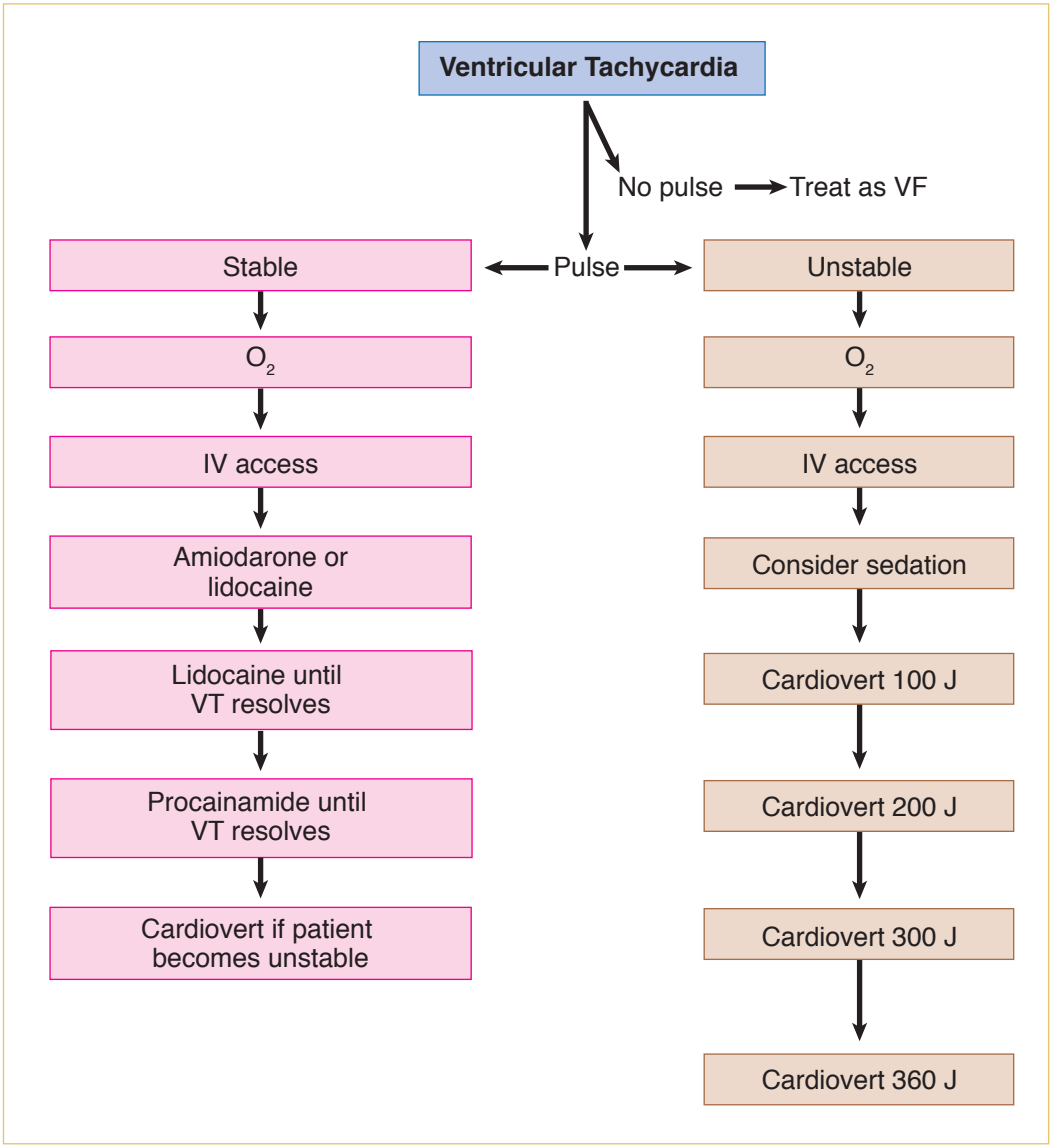


Figure 5-17. Management of VT

Clinical Recall

Which of the following is the most appropriate management for Wolf-Parkinson-White syndrome?

A. Procainamide
B. Propranolol
C. Verapamil
D. Nimodipine
E. Sotalol

Answer: A

Torsade de Pointes

Torsade de Pointes, a type of VT, is characterized by undulating rotations of the QRS complexes around the electrocardiographic baseline. Arrhythmias are initiated by a ventricular premature beat in the setting of abnormal ventricular repolarization characterized by prolongation of the QT interval.

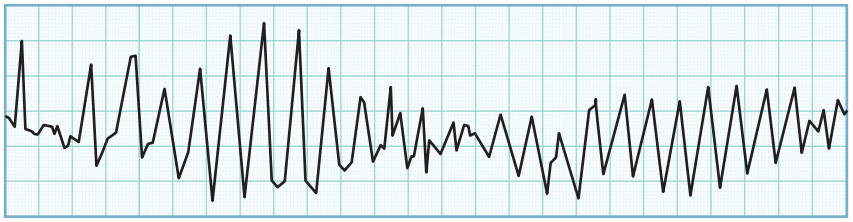


Figure 5-18. Torsade de Pointes

Causes of torsade include antiarrhythmic drugs which prolong ventricular repolarization:

- Antiarrhythmics: quinidine, procainamide, disopyramide
- Psychotropic drugs: phenothiazines, thioridazine, tricyclics, lithium
- Electrolyte imbalance: hypokalemia, hypomagnesemia
- CNS lesion: subarachnoid or intracerebral hemorrhage

Patients with long QT interval syndrome are prone to recurrent dizziness or syncope from the ventricular tachycardia. Sudden auditory stimuli, such as the ringing of the telephone at night, may initiate torsade in these patients.

Treatment addresses the underlying disorder. For the antiarrhythmics, use a drug such as lidocaine. For the electrolyte imbalances, replace potassium and magnesium. Cardiac pacing or isoproterenol infusion may suppress episodes of tachycardia, useful for emergency treatments.

If patient is hemodynamically unstable (e.g., hypotension), consider cardioversion (but this dysrhythmia often reoccurs).

Ventricular Fibrillation

See the Emergency Medicine section.

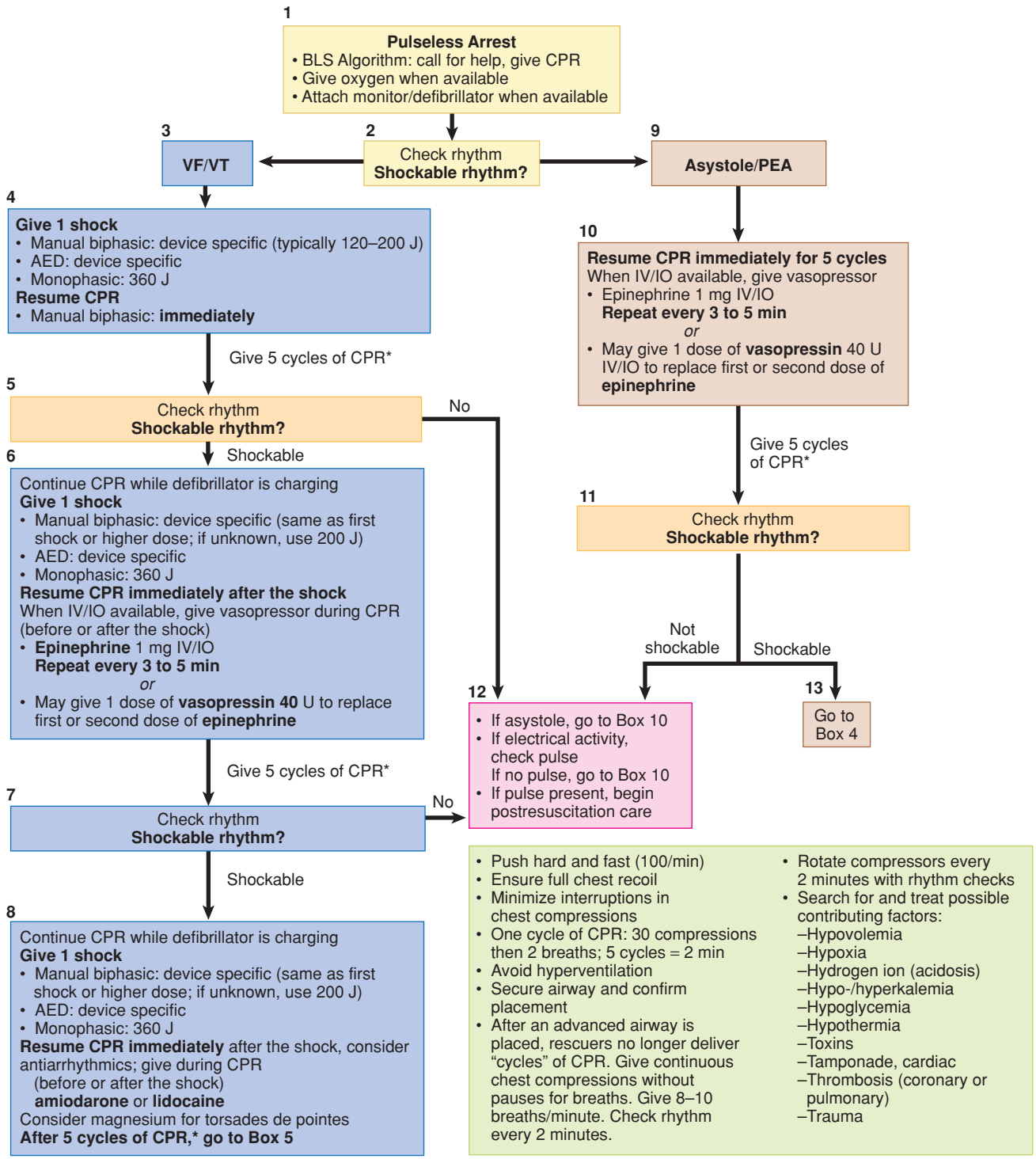


Figure 5-19. ACLS Pulseless Arrest Algorithm

DRUGS FOR CARDIOVASCULAR DISEASE

Amiodarone

Amiodarone is a very effective antiarrhythmic drug and can be used in ventricular tachycardia, Afib, and atrial flutter. Because it has a long half-life (>50 days), drug interactions are possible for weeks after discontinuation.

Side effects may be severe, even fatal:

- **Lungs**: severe interstitial disease with hypoxia, cough, fever, and chest pain
- **Nervous** (20%): abnormal gait, coordination, and balance, tremor, muscle weakness, numbness
- **Thyroid**: hypo- or hyperthyroidism (the drug is structurally similar to thyroxine)
- **Dermatology**: photosensitivity, blue-grey skin discoloration
- **Eye**: visual loss, blurriness, halos, corneal deposits

Nitrates

In **low doses**, nitrates increase venous dilation and subsequently reduce preload. In **medium doses**, they increase arteriolar dilatation and subsequently decrease afterload and preload. In **high doses**, they increase coronary artery dilatation and subsequently increase oxygen supply.

Side effects of nitrates include orthostatic hypotension, reflex tachycardia, throbbing headache, and blushing—all caused by vasodilation. Nitrates are contraindicated if systolic BP <90 mm Hg. There must be a window-free period of >8 hours with nitrate therapy to reduce the incidence of tachyphylaxis.

Antiarrhythmics

Table 5-15. Antiarrhythmic Drugs

Drug	Adverse Effects
Disopyramide	Anticholinergic effects; hypotension; heart failure; heart block; tachyarrhythmia
Lidocaine	CNS (drowsiness, agitation, seizures); heart block
Phenytoin	CNS (ataxia, nystagmus, drowsiness); hypotension and heart block with rapid IV injection
Procainamide	Lupus-like syndrome; GI; rash; hypotension; aggravation of arrhythmia; blood dyscrasias
Quinidine	Aggravation of arrhythmias ("quinidine syncope"); thrombocytopenia; fever, rash; cinchonism; GI symptoms; digoxin-quinidine interaction (elevation of digoxin levels)
β-adrenergic blocking agents	Heart block; hypotension; asthma; hypoglycemia; lethargy; impotence
Verapamil	CHF, asystole, constipation
Adenosine	Transient dyspnea, noncardiac chest pain, rarely hypotension
Mexiletine	Lidocaine-like drug; local anesthetic
Tocainide	Lidocaine-like drug
Amiodarone	Very long half-life (20–40 d); may increase digoxin level; may worsen existing cardiac conduction disturbances; may prolong Coumadin effect
Encainide	Negative inotropism; QRS and PR prolongation
Flecainide	Negative inotropism; QRS and PR prolongation
Propafenone	Negative inotropism; QRS and PR prolongation

Beta Blockers

Beta blockers (BBs) have been shown to improve survival after an acute MI and in CHF. They decrease heart rate, BP, and contractility, which decrease myocardial oxygen requirement.

BBs are safe in most patients with asthma and should be used in asthma if indicated (EF <40% or CAD).

Nonselective BBs may mask hypoglycemic symptoms in insulin-dependent diabetics.

- BBs can cause fatigue/insomnia, mental depression, lipid abnormalities, hallucinations, Raynaud phenomenon, bronchoconstriction, and sexual dysfunction.
- BBs can mask signs/symptoms of insulin-induced hypoglycemia.
- Nebivolol is a unique BB; it is a beta-1 specific blocker that increases nitric oxide and thus does not cause erectile dysfunction.

Table 5-16. Pharmacologic Properties of Select β-Blocking Agents

Name	Cardio-Selective
Metoprolol	Yes
Atenolol	Yes
Propranolol	No
Nadolol	No
Timolol	No
Pindolol	No
Acebutolol	Yes
Labetalol	No
Esmolol (IV)	Yes

Calcium Channel Blockers

Calcium channel blockers (CCBs) work by decreasing preload and afterload. They may be harmful in the postinfarction period, especially if the patient has left ventricular failure. Their efficacy in angina is very limited—there is no mortality benefit.

Note

In HFrEF:

- Verapamil and diltiazem should not be used.
- Amlodipine and felodipine are safe and can be used.

Side effects of CCBs can be cardiac or noncardiac.

- **Cardiac**: CHF, reflex tachycardia, hypotension, lightheadedness, AV block
- **Noncardiac**: flushing, headache, weakness, constipation, nasal congestion, wheezing, peripheral edema, gingival hyperplasia

SHOCK SYNDROMES

Shock is a broad term that describes a state where oxygen delivery to the tissues is inadequate to meet the demands. It could be described as the imbalance between tissue oxygen supply and demand.

Four general types of shock syndromes are recognized: distributive, cardiogenic, hypovolemic, and obstructive. There are many etiologies within each class.

Note

Septic shock is most common form of shock among those admitted to the ICU, followed by cardiogenic and hypovolemic shock.

- **Distributive shock:** caused by pathologic peripheral blood vessel vasodilation; examples are sepsis (especially gram-negative), anaphylaxis, neurogenic
- **Cardiogenic shock:** related to impaired heart pump function; examples are acute coronary syndrome, valve failure (especially acute) and dysrhythmia
- **Hypovolemic shock:** caused by decreased circulatory volume; examples are hemorrhage (GI bleed) and fluid loss
- **Obstructive shock:** non-cardiac obstruction to blood flow; examples are pulmonary embolus, tension pneumothorax, and cardiac tamponade

The diagnosis of shock is a clinical diagnosis.

Table 5-17. Physiologic Characteristics of Various Forms of Shock

Type of Shock	Heart Rate	Central Venous Pressure	Contractility	Systemic Vascular Resistance
Cardiogenic	↑	↑	↓↓	↑
Hypovolemic	↑	↓↓	±↑	↑
Distributive (sepsis)	↑	↓↓	±	↓
Obstructive	↑	±↑	±	↑ (tamponade, PE) ↑ (tension PTX)

In shock, cardiac output varies, **increasing** in the hyperdynamic state of distributive shock (and sometimes in hypovolemic shock depending on how much volume has been lost), but is always **decreasing** in cardiogenic shock. Treatment should begin quickly, since delayed therapy worsens outcomes.

- Start with ABCs and consider intubation for airway protection and to enhance ventilation and oxygenation, given the high incidence of cardiogenic and non-cardiogenic pulmonary edema.
- Maximize arterial oxygen saturation.
- Circulatory support with normal saline or blood is used early. (The exception might be in cardiogenic shock with pulmonary edema where ECV is already expanded.)
- Blood transfusion is the norm in traumatic hypovolemic shock.
- Hypotensive patients who do not respond to saline or blood will need pressor support: dopamine, vasopressin, or epinephrine in distributive shock, and dobutamine in cardiogenic shock.
- Hypotensive patients with septic shock who do not respond promptly to saline should be given norepinephrine and vasopressin.
- A single dose of hydrocortisone should be given if patient is still hypotensive on pressors, since adrenal insufficiency is common in severely ill patients. An ACTH stimulation test can also be done quickly to diagnose unsuspected adrenal failure.

Clinical Recall

Which of the following is a side effect of amiodarone?

A. Constipation

B. Orthostatic hypotension

C. Pulmonary fibrosis

D. Thrombocytopenia

E. Major depression

Answer: C

Hematology 6

Learning Objectives

- ❏ List the types of anemia and describe their pathophysiology, diagnosis, and treatment
- ❏ Describe the presentation and diagnosis of hematologic neoplasias including acute leukemia, chronic leukemias, plasma cell disorders, and lymphomas
- ❏ Describe common platelet disorders
- ❏ List defects that can occur in the coagulation cascade and their associated disorders

ANEMIA

Anemia is caused by a lack of (or impaired) RBCs in the body, resulting in a decreased flow of oxygen to the organs. It is marked by one of the following:

- Hematocrit <41% in men or <36% in women
- Hemoglobin <13.5 g/dL in men or <12 g/dL in women

Anemia is most easily classified according to cell size.

- **Microcytic anemia** is characterized by a low mean corpuscular volume (MCV) <80, most commonly caused by iron deficiency, thalassemia, sideroblastosis, lead poisoning, or anemia of chronic disease (either microcytic or normocytic).
- **Macrocytic anemia** is characterized by an elevated MCV >100, most commonly caused by vitamin B12 or folic acid deficiency but also caused by the toxic effects of alcohol, liver disease, or chemotherapeutic agents (e.g., methotrexate, AZT, phenytoin).
- **Normocytic anemia** is characterized by a normal MCV, most commonly caused by the early form of the conditions described, plus hemolysis and aplastic anemia.

The symptoms of anemia tend to be based on the severity of the anemia, rather than the etiology.

- Early symptoms include fatigue and poor exercise tolerance.
- As the anemia worsens, there is dyspnea on exertion and lightheadedness.
- Eventually, confusion and altered mental status may develop as oxygen delivery to the brain decreases.
- Death from anemia is most often caused by decreased oxygen delivery to the heart and resulting myocardial ischemia.

The severity of symptoms is related to the patient's underlying condition. A healthy young patient may have no symptoms at all with hematocrit 27–29%, while an older patient with heart disease may develop dyspnea or anginal symptoms with the same hematocrit.

Diagnosis. Once a diagnosis of anemia is determined based on a low hematocrit or hemoglobin, the first step is to determine the MCV. Iron studies, reticulocyte count, peripheral smear, red cell distribution width (RDW), Coombs test, vitamin B12, folate level, and even a possible bone marrow biopsy may be necessary to determine a specific etiology.

Treatment. Besides blood transfusion, treatment cannot be generalized. Packed RBCs are used to maintain a hematocrit >25–30%. This is based on the underlying condition of the patient. A healthy young patient can have transfusion withheld until hematocrit is in the low 20%. An older patient with coronary artery disease will need to be maintained when hematocrit >30%. Hematocrit should rise approximately 3 points for every unit of packed RBCs given. Whole blood is rarely, if ever, used.

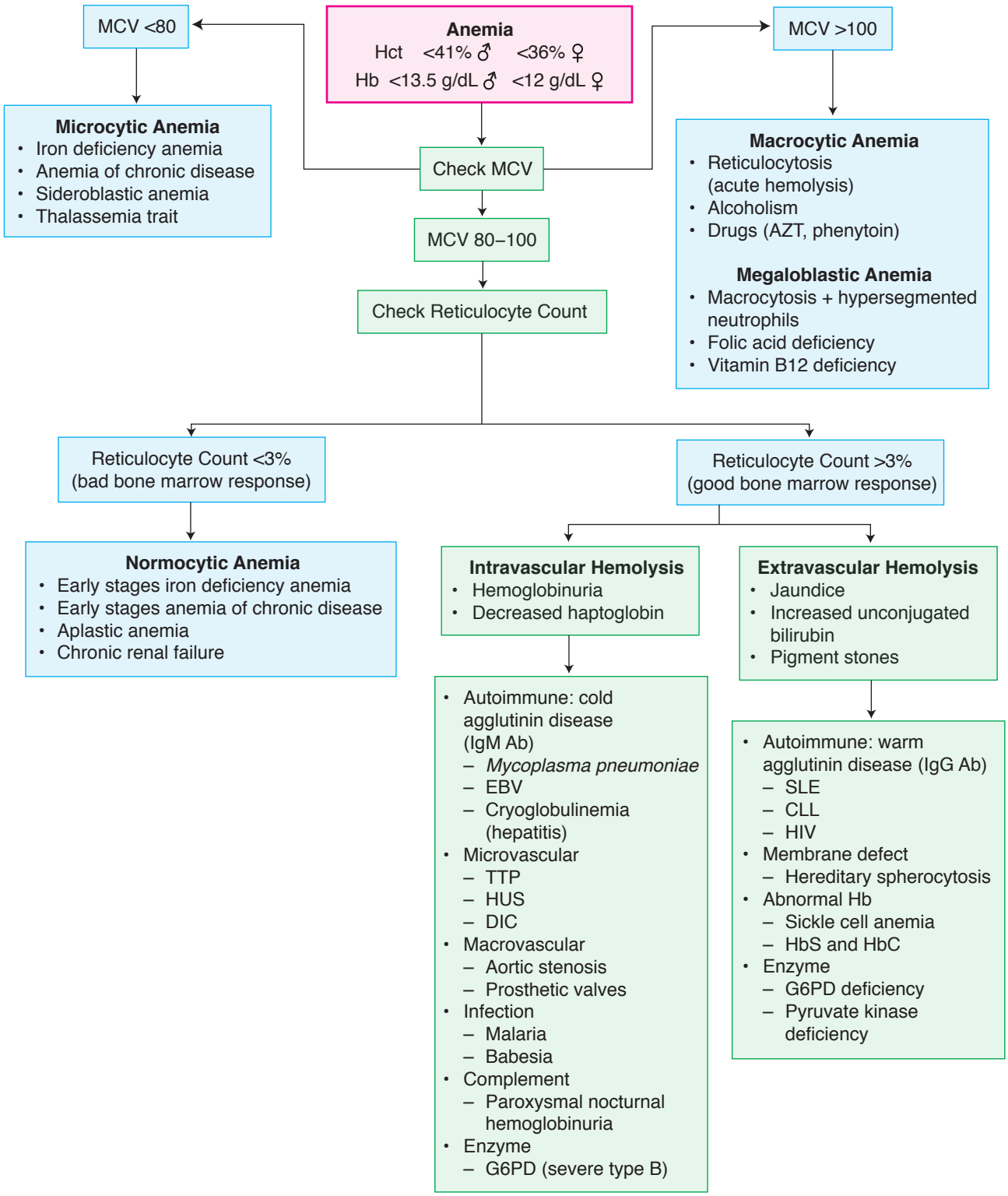


Figure 6-1. Evaluation of Patients with Anemia

Microcytic Anemia

Iron Deficiency Anemia

Iron deficiency anemia is anemia with diminished RBC production and MCV <80, characterized by hypochromic cells and low levels of stored iron. It is almost always caused by blood loss, most commonly GI or menstrual.

Iron absorption is tightly regulated. A man requires 1 mg per day and a woman 2–3 mg per day on average. It is difficult for the body to increase the level of iron absorption. If there is even a modest increase in blood loss—occult blood in the stool, heavier menstrual flow, or increased demand such as in pregnancy—the body is poorly equipped to increase its level of absorption to exceed 3–4 mg per day. Other etiologies are increased urinary loss of blood, malabsorption, hemolysis, and poor oral intake.

Clinical Presentation. Mild anemia may have no or very limited symptoms. As hematocrit approaches 30%, fatigue and poor exercise tolerance may develop. As hematocrit lowers to 25%, tachycardia, palpitations, dyspnea on exertion, and pallor develop. Older patients and those with coronary artery disease may become dyspneic at higher levels of hematocrit. More severe anemia results in lightheadedness, confusion, syncope, and chest pain. A systolic ejection murmur ("flow" murmur) may develop in any patient with moderately severe anemia. These symptoms are not specific for iron deficiency anemia and may develop with any form of anemia provided it is sufficiently severe.

Symptoms specific to iron deficiency are rare and cannot be relied upon to determine the diagnosis: brittle nails, spoon-shaped nails, glossitis, and pica. Iron deficiency anemia as a specific diagnosis is determined by laboratory findings, not symptoms.

Clinical Pearl

In early iron deficiency, serum iron may be normal. (Ferritin is low and TIBC is elevated.)

Diagnosis. A low serum ferritin <10 ng/mL is the most characteristic finding of iron deficiency anemia. Low ferritin has good specificity (>99%) but poor sensitivity (60%); the ferritin level may be falsely elevated because it is an acute phase reactant and may be elevated in other inflammatory states or with malignancy. MCV is low except in very early cases. The serum iron is low and the total iron binding capacity (TIBC) is high. The RDW is elevated. The most specific test, although rarely necessary, is a bone marrow biopsy looking for stainable iron stores. The reticulocyte count is low. Platelet levels rise.

Treatment.

- Oral therapy with ferrous sulfate tablets, continued until Hb and Hct have normalized + an additional 2–3 months to "restore" iron stores (a brisk increase in reticulocytes will be seen 2 weeks into treatment)
- Parenteral iron for those with malabsorption, kidney disease, or an intolerance to oral therapy
- Blood transfusion (most effective way to deliver iron) only for those with severe symptoms

Aside from iron replacement, it is imperative to look for the source of the iron loss (i.e., GI, gynecological, or rarely urinary).

Anemia of Chronic Disease

Anemia of chronic disease is a defect in the body's ability to make use of iron sequestered in stores within the reticuloendothelial system. It can be microcytic or normocytic. Anemia can accompany virtually any chronic inflammatory, infectious, or neoplastic condition.

Hepcidin, a regulator of iron metabolism, plays an important role in this condition.

- In states where hepcidin is **abnormally high** (e.g., inflammation), serum iron falls due to iron trapping within macrophages and liver cells and decreased gut iron absorption. This typically leads to anemia caused by an inadequate amount of serum iron being available for developing red cells.
  - Hepcidin inhibits iron transport by binding to the iron export channel ferroportin located on the surface of gut enterocytes and the plasma membrane of macrophages.
  - The ferroportin inhibition has the following results:
    - Prevents iron from being exported and it is instead sequestered in the cells
    - Prevents enterocytes from allowing iron into the hepatic portal system, thereby reducing dietary iron absorption
    - Reduces the iron release from macrophages
- In genetic diseases where hepcidin is **abnormally low**, iron overload may occur (hemochromatosis) due to unwarranted ferroportin facilitated iron influx.

Clinical Presentation. Symptoms are based on the severity of the anemia. The only other symptoms are based on the specifics of the underlying disease.

Diagnosis.

- Normal or elevated serum ferritin
- Low serum iron
- Low TIBC
- Low reticulocyte count

Treatment. Correct the underlying disease.

- Iron supplementation and erythropoietin will not help, except in renal disease and anemia caused by chemotherapy or radiation therapy.
- Transfusion of packed RBCs is not generally used unless hemoglobin <7 g/dL.

Sideroblastic Anemia

Sideroblastic anemia is a microcytic anemia caused by a disorder in the synthesis of hemoglobin, characterized by trapped iron in the mitochondria of nucleated RBCs.

- The **hereditary form** is due to a defect in aminolevulinic acid synthase or an abnormality in vitamin B6 metabolism.
- The **acquired form** is due to drugs such as chloramphenicol, isoniazid, or alcohol. Lead poisoning can cause sideroblastic anemia as well.

There is an association with myelodysplastic syndromes and refractory anemia. Sideroblastic anemia may progress to acute myelogenous leukemia in a small percentage of patients.

Clinical Presentation. Symptoms are related to the severity of the anemia. There is no specific finding that will be sufficiently suggestive of sideroblastic anemia to allow a diagnosis without significant lab evaluation.

Note

Anemia of chronic disease often starts as a normocytic anemia and becomes slightly microcytic over time.

Note

- Iron deficiency and anemia of chronic disease can cause **decreased serum iron**.
- Sideroblastic anemia is the only microcytic anemia that causes **elevated serum iron**.

Diagnosis.

- Elevated serum ferritin
- Very high transferrin saturation, and very low TIBC
- High serum iron (**the only microcytic anemia with elevated iron**)
- Prussian Blue stain (**most specific test**) of RBCs in the marrow will reveal the ringed sideroblasts
- Strikingly high marrow reticuloendothelial

Treatment. Remove the offending drug. Some patients, especially those with INH-associated sideroblastic anemia, will respond to pyridoxine therapy 2-4 mg per day. Consider transfusion for serious cases and BMT for refractory cases. If the patient has lead intoxication, use chelators (patient should refrain from the use of alcohol).

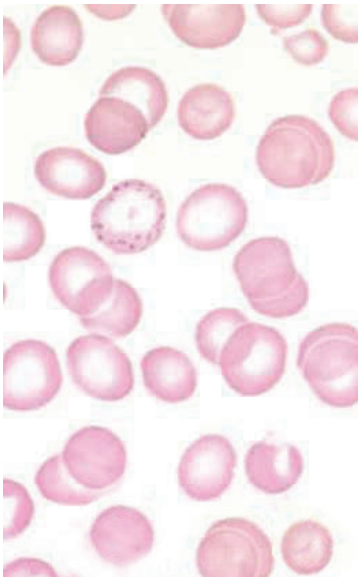


Figure 6-2. Basophilic Stippling, a Feature of Lead Poisoning and Other Diseases

Thalassemia

Thalassemia is a hereditary underproduction of either the alpha or beta globin chains of the hemoglobin molecule, resulting in a hypochromic, microcytic anemia. Gene deletion results in variable levels of disease.

There are 4 genes coding for the alpha chain of hemoglobin. There can be deletions of 1, 2, 3, or all 4 genes.

- Beta thalassemia can be mutated in either 1 or 2 genes.
- Alpha thalassemia is more common in Asian populations, while beta thalassemia is more common in Mediterranean populations.

Clinical Presentation. Presentation depends on the number of abnormal genes.

- **Alpha thalassemia**
  - 1 gene deletion yields a normal patient; CBC, hemoglobin, and MCV are normal.
  - 2 gene deletion yields a mild anemia with hematocrit 30–40% and strikingly low MCV.
  - 3 gene deletion yields a more profound anemia with hematocrit 22–32% and very low MCV.
  - 4 gene deletion alpha thalassemia causes patients to die in utero, secondary to gamma chain tetrads called hemoglobin Barts.
- In **beta thalassemia** trait there is a mild anemia with marked microcytosis (low MCV).
  - Patients with beta thalassemia major (or Cooley's anemia) are homozygous for mutations of both genes coding for the beta hemoglobin gene. Patients become severely symptomatic starting age 6 months, when the body would normally switch from fetal hemoglobin to adult hemoglobin. They are severely symptomatic with growth failure, hepatosplenomegaly, jaundice, and bony deformities secondary to extramedullary hematopoiesis. They are later symptomatic from hemochromatosis, cirrhosis, and CHF from chronic anemia and transfusion dependence.

Diagnosis. Clues to the diagnosis of thalassemia trait is a mild anemia with a profound microcytosis. Beta thalassemia major has the severe symptoms, large spleen, and bone abnormalities described. Both forms of thalassemia are diagnosed by having a microcytic anemia with normal iron studies. Hemoglobin electrophoresis differentiates which type of thalassemia is present. In beta thalassemia, there is an increased level of hemoglobin F and hemoglobin A2. In beta thalassemia major, the hemoglobin is as low as 3–4 g/dL. Those with alpha thalassemia will have normal amounts of hemoglobins F and A2. Tetrads of beta chains are called hemoglobin H. Hemoglobin H is present in alpha thalassemia with 3 of 4 genes deleted. Target cells are present in all forms of thalassemia trait and thalassemia major. The RDW is normal in all forms because all of the cells are of the same size. Thalassemia is the only anemia where the RBC count is normal or even high. Thus, while patients have a low hemoglobin, the total number of RBCs is normal to elevated.

Treatment. Thalassemia traits of both the alpha and beta types do not require specific treatment. Beta thalassemia major patients require blood transfusions once or twice a month. The chronic transfusions lead to iron overload, which requires treatment with deferasirox. Oral deferasirox is the standard of care. This is easier to give than deferoxamine, which requires a subcutaneous pump. Splenectomy eliminates a major area of hemolysis and therefore helps reduce transfusion requirements. A small number of patients can be treated with a bone marrow transplantation.

Clinical Pearl

Thalassemia trait syndromes are asymptomatic.

Table 6-1. Iron Indices in Microcytic Anemia Syndromes

Fe Panel	Iron Deficiency Anemia	Anemia of Chronic Disease	Sideroblastic Anemia	Thalassemia Minor
Serum Iron	Decreased	Decreased	Increased	Normal
Serum Ferritin	Decreased or Normal (early)	Increased	Increased	Normal
Transferrin/ TIBC	Increased	Decreased	Decreased	Normal
% Saturation	Decreased	N/Decreased	Increased	Normal

Clinical Recall

Which of the following laboratory investigations has the highest specificity and sensitivity in the diagnosis of iron deficiency anemia?

A. Serum ferritin level

B. Serum iron level

C. Serum TIBC

D. Serum MCV

E. Bone marrow biopsy

Answer: E

Macrocytic Anemia

A 72-year-old alcoholic man presents with several weeks of memory loss and tingling in his feet. His hematocrit is 32% and MCV 110.

Vitamin B12 (Cyanocobalamin) Deficiency

Vitamin B12 deficiency is decreased absorption or intake of B12, resulting in hematologic and/or neurologic abnormalities.

Causes include:

- Pernicious anemia (**most common**), a disorder causing decreased intrinsic factor production due to autoimmune destruction of parietal cells
  - Gastrectomy and atrophic gastritis can also decrease intrinsic factor production.
  - The incidence of pernicious anemia increases with age.

- Forms of malabsorption, e.g., sprue, regional enteritis, and blind loop syndrome
- Pancreatic insufficiency
- Tapeworm infection with *Diphyllobothrium latum* (rarely the cause)
- Certain medications

Symptoms vary with the severity of the anemia. As such, diagnosis of B12 deficiency cannot be made only from the symptoms of anemia.

Symptoms include hematologic and neurologic deficits—seen individually or combined.

- Neurologic manifestations (at almost any level of neurologic system): peripheral neuropathy, position sense abnormality, vibratory, psychiatric, autonomic, motor, cranial nerve dysfunction
- Bowel/bladder dysfunction
- Sexual dysfunction
- Possible glossitis, diarrhea, and abdominal pain

Diagnosis.

- Anemia with macrocytosis (increased MCV)
- Neurologic deficits (a small number of patients have these alone)
- WBCs with hypersegmented neutrophils and mean lobe count >4
- RBCs characterized by macro-ovalocytes
- Reduced reticulocyte count, with hypercellular bone marrow
- Possible pancytopenia
- Possible elevated LDH, bilirubin, and iron as a result of mild hemolysis of immature erythrocytes within the bone marrow (in some cases LDH may be very elevated)
- Elevated methylmalonic acid (useful if B12 level is equivocal)

While the low B12 level (most specific test) confirms diagnosis, the antibodies to intrinsic factor and parietal cells confirm the etiology as pernicious anemia.

The Schilling test is rarely used to determine the etiology of vitamin B12 deficiency. It is not necessary if the patient has a low B12 plus antibodies to intrinsic factor.

Treatment.

- Replacement of vitamin B12 (lifelong); response is rapid, with reticulocytosis seen in 2–5 days and hematocrit normalizing within weeks
  - Oral (daily) intake
  - Parenteral (monthly intramuscular or subcutaneous) preparations (**recommended for those with neurologic symptoms**)
- Cobalamin to halt progression of the B12 deficiency process (but will not fully reverse more advanced neurologic effects)
- Treat the underlying etiology of the B12 deficiency if possible (e.g., fish tapeworm infection, bacterial overgrowth).
- Folic acid replacement to correct the hematologic abnormalities of B12 deficiency (but will not fully reverse more advanced neurologic effects)

Note

The hematologic pattern of B12 deficiency is indistinguishable from that of folate deficiency.

Note

- Although macrocytosis can occur with hemolysis, liver disease, and myelodysplasia, these produce **round macrocytes**.
- B12 and folate deficiency produce **oval macrocytes**.

Note

Once parenteral loading of B12 has been initiated, long-term B12 replacement is usually the oral form. This is quite effective, cheaper, and easier for the patient. IV replacement is not recommended because too much of the vitamin would be lost in the urine.

If megaloblastic anemia accompanies the B12 deficiency, early treatment might lead to severe hypokalemia and fluid overload due to increased erythropoiesis, cellular uptake of potassium, and increased blood volume. Once patients are treated for they B12 deficiency, lifelong cobalamin therapy will be required.

Folic Acid Deficiency

Folic acid deficiency is almost always caused by some form of decreased dietary intake. It can lead to anemia. Occasionally, increased requirements from pregnancy, skin loss in diseases like eczema, or increased loss from dialysis and certain anticonvulsants such as phenytoin may occur. Consumption of high amounts of alcohol may have a direct effect on the folate absorption, due to inhibition of the enzyme intestinal conjugase. Folate is presented in foods as polyglutamate, which is then converted into monoglutamates by intestinal conjugase.

Clinical Presentation. Presentation depends entirely on the severity of the anemia.

Diagnosis. The hematologic presentation of folic acid deficiency is identical to B12 deficiency. The diagnosis is based on a low red-blood-cell, folic acid level.

Treatment is folic acid replacement, almost always orally.

Normocytic Anemia

Hemolysis

Hemolytic anemias are caused by decreased RBC survival from increased destruction of the cells. The destruction may be inside the blood vessels (intravascular) or outside (extravascular), which generally means inside the spleen. Hemolytic anemia may be **chronic** (sickle cell disease, paroxysmal nocturnal hemoglobinuria, and hereditary spherocytosis) or **acute** (drug-induced hemolysis, autoimmune hemolysis, or glucose 6-phosphate dehydrogenase deficiency).

Table 6-2. Classification of Hemolytic Anemias

Hereditary Anemias	Acquired Anemias
Membrane: hereditary spherocytosis, hereditary elliptocytosis	**Immune** • **Autoimmune:** warm antibody type, cold antibody type • **Alloimmune:** hemolytic transfusion reactions, hemolytic disease of the newborn, allografts (especially stem cell transplantation) • **Drug-associated**
Metabolism: G6PD deficiency, pyruvate kinase deficiency	**Red Cell Fragmentation Syndromes**
Hemoglobin: genetic abnormalities (Hb S, Hb C, unstable)	**Infections**: malaria, clostridia
	Chemical and Physical Agents: drugs, industrial/domestic substances, burns
	Secondary: liver and renal disease
	Paroxysmal Nocturnal Hemoglobinuria

Clinical Presentation. The usual symptoms of anemia are present based on the severity of the disease, not necessarily the etiology. Fatigue and weakness occur with mild disease. Dyspnea and later confusion occur with more severe disease. The major difference between hemolytic anemia and the micro- and macrocytic anemias is that hemolysis is more often the etiology when the onset is sudden. This is, of course, provided that simple blood loss has been excluded. Hemolysis is often associated with jaundice and dark urine as well. Specific findings associated with each disease are described. Fever, chills, chest pain, tachycardia, and backache may occur if the intravascular hemolysis is particularly rapid.

Diagnosis. Patients with hemolytic anemias generally have a normal MCV, but the MCV may be slightly elevated because reticulocytes are somewhat larger than older cells. The reticulocyte count is elevated. The LDH and indirect bilirubin are elevated. Bilirubin levels above 4 are unusual with hemolysis alone. The peripheral smear may aid in the specific diagnosis, and the haptoglobin may be low with intravascular hemolysis. Hemoglobin may be present in the urine when intravascular hemolysis is sudden and severe because free hemoglobin spills into the urine. There should not be bilirubin in the urine because indirect bilirubin is bound to albumin and should not filter through the glomerulus. Hemosiderin is a metabolic product of hemoglobin. Hemosiderin may be present in the urine if the hemolysis is severe and lasts for several days.

Treatment. Transfusion is needed as in all forms of anemia when the hematocrit becomes low. Hydration is, in general, useful to help prevent toxicity to the kidney tubule from the free hemoglobin. Specific therapy is discussed with each disease. Patients with chronic hemolytic anemia need to be maintained on chronic folic acid therapy, as there is an increase in cell turnover.

Sickle Cell Disease

Sickle cell disease is a hereditary form of chronic hemolysis, ranging from asymptomatic to severe, overwhelming crisis. It is characterized by irreversibly sickled cells and recurrent painful crises.

- Autosomal recessive hereditary disease
- Hemoglobin S is due to a substitution of a valine for glutamic acid as the sixth amino acid of the beta globin chain.
- **Heterozygous form (trait)** (8% of African-Americans); all those with the trait are asymptomatic
- **Homozygous form (disease)** (1 in 400 African-Americans)
- A sickle cell acute painful crisis may be precipitated by hypoxia, dehydration, acidosis, infection, and fever. However, the crisis may occur without the presence of these factors.
- Sickle cell crisis is usually not associated with an increase in hemolysis or drop in hematocrit.
  - If increased hemolysis occurs, consider another etiology such as concomitant glucose 6 phosphate dehydrogenase deficiency (G6PD) or acute splenic sequestration in a child.
  - If a sudden drop in hematocrit occurs, consider another etiology such as Parvovirus B19 infection or folate deficiency. The drop in hematocrit is from acute aplasia (decrease in cell production), not from hemolysis.

Note

The **acute chest syndrome** seen in sickle cell disease is indistinguishable from pneumonia. It is a life-threatening manifestation of sickle cell disease.

Clinical Presentation.

- **Acute crisis**
  - Back, rib, chest, and leg pain
  - Possible manifestations of sickling (production of sickle-shaped RBCs) may be severe and life-threatening:
    - Acute chest syndrome (severe chest pain, fever, leukocytosis, hypoxia, and lung infiltrates on chest x-ray) causing infarction and infection
    - Atelectasis (common) as a result of the pain with infection
- **Chronic disease**
  - Renal concentrating defects (isosthenuria)
  - Hematuria
  - Ulcerations of the skin on the legs
  - Bilirubin gallstones
  - Aseptic necrosis of the femoral head
  - Osteomyelitis,
  - Retinopathy
  - Recurrent infections from *Pneumococcus* or *Haemophilus*
  - Growth retardation
  - Splenomegaly (followed in adulthood by autosplenectomy)

Treatment is incentive spirometry, pain control, antibiotics and oxygen. If no response, consider exchange transfusions.

Stroke and TIA may also occur. Priapism can occur from infarction of the prostatic plexus of veins. Blindness and even myocardial infarction and cardiomyopathy may also occur. Pregnant patients experience increased rates of spontaneous abortion and low birth weight.

Sickle trait gives normal hematologic picture with no anemia and a normal MCV. The only significant manifestation of trait is the renal concentrating defect presenting with isosthenuria and **microscopic hematuria**. Sickle trait also increases the frequency of UTI. Those with trait will rarely develop the acute pain crisis under conditions of profound hypoxia and acidosis.

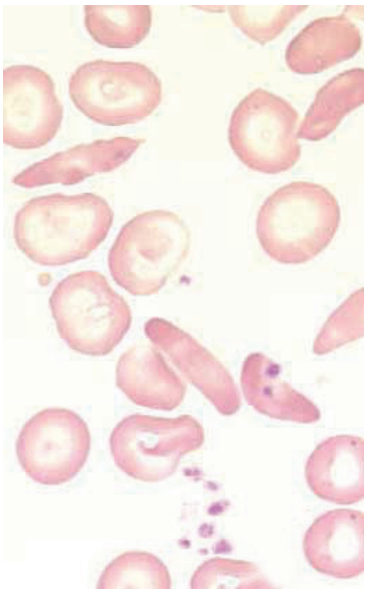


Figure 6-3. Sickle Cells Noted on a Peripheral Blood Smear

Diagnosis. Patients with sickle cell disease typically have a mild to moderate anemia with a normal MCV. The reticulocyte count should always be elevated in the 10–20% range unless they have folate deficiency or Parvovirus B19 aplastic crisis. LDH and bilirubin are elevated as in all types of hemolytic anemias. The hemoglobin electrophoresis is the most specific test. The peripheral smear shows sickled cells. The sickle prep (or Sickledex) is a quick screening test used to diagnose evidence of sickle cell trait and cannot distinguish between trait and homozygous disease. The urinalysis usually has blood present, although it is often microscopic. The white blood cell count is often elevated in the 10,000–20,000 range, although this can also indicate the presence of infection.

Treatment.

- **Acute crisis**: fluids, analgesics, and oxygen
  - For any infection, or even for fever + leukocytosis but no identified site of infection: antibiotics (ceftriaxone is preferred because it covers *Pneumococcus* and *H. influenza*)
  - For severe/life-threatening manifestations: RBC transfusion if hematocrit is low, and exchange transfusion if hematocrit is high
- **Chronic disease**
  - Folic acid replacement
  - Vaccinations against *Pneumococcus* and influenza
  - Hydroxyurea to decrease the frequency of the vaso-occlusive pain crisis
  - Bone marrow transplantation (curative) for severe cases
  - Exchange transfusion for stroke, priapism, acute chest syndrome and sickle cell patients going into labor or a surgical procedure

Autoimmune, Cold Agglutinin, and Drug-Induced Hemolytic Anemia

Various forms of acquired hemolytic anemia can result from the production of IgG, IgM, or activation of complement C3 against the red cell membrane. They are often sudden and idiopathic. The lysis can be intravascular or extravascular (far more common). That is because the destruction of the cells most often occurs through macrophages in the spleen or by Kupffer cells in the liver.

Autoimmune destruction is often idiopathic. Known causes of autoimmune destruction are from antibodies produced in relationship to various forms of leukemia, especially chronic lymphocytic leukemia, viral infections, lymphoma, collagen vascular diseases like lupus, or in relationship to drugs. The most common drugs are the penicillins, cephalosporins, sulfa drugs, quinidine, alpha-methyldopa, procainamide, rifampin, and thiazides.

Ulcerative colitis can also lead to autoimmune hemolytic anemia.

- **Cold agglutinin** disease is an IgM antibody produced against the red cell in association with malignancies such as lymphoma or Waldenstrom macroglobulinemia and infections such as *Mycoplasma* or mononucleosis. Cold agglutinin destruction occurs predominantly in the liver. Liver-mediated destruction is not affected by steroids. Up to 50% of patients do not have an associated underlying disorder.
- Autoimmune hemolytic anemia due to a **warm agglutinin** (an IgG) is more aggressive often due to SLE, lymphoma, CLL and medications. This can lead to severe hemolysis and requires high doses of corticosteroids followed by other immunomodulating agents. In intractable cases, splenectomy is needed.

Clinical Presentation. Symptoms are generally related to the severity of the anemia, not the etiology. The onset may be very sudden, resulting in fever, syncope, congestive failure, and hemoglobinuria. Mild splenomegaly is present when the disease has been occurring long enough for the time it takes for the spleen to enlarge. The drug history is often the clue with drug-induced varieties. Cold agglutinin disease results in cyanosis of the ears, nose, fingers, and toes. Weakness, pallor, jaundice, and dark urine may occur as it can in all forms of hemolysis of sufficient severity.

Diagnosis. Autoimmune hemolysis gives a normocytic anemia, reticulocytosis, increased LDH, absent or decreased haptoglobin, and increased indirect bilirubin, as can all forms of hemolysis. The Coombs test is the specific test that diagnoses autoimmune, cold agglutinin, and often even drug-induced hemolysis. Spherocytes are often present on the smear.

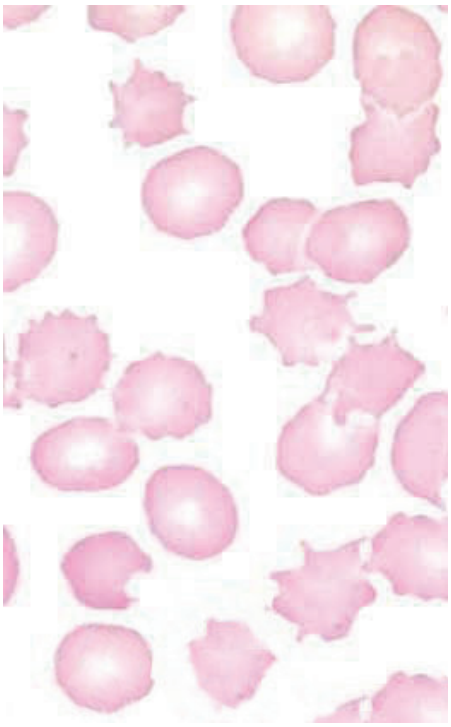


Figure 6-4. Acanthocytes, a Feature of Several Hematologic and Systemic Diseases

Treatment. Mild disease often occurs, which needs no treatment. In cases of drug-induced hemolysis, stop the offending drug. More severe autoimmune hemolysis is treated with steroids first. Splenectomy is done for those unresponsive to steroids. Cold agglutinin disease is primarily managed by avoiding the cold. Most cases of cold agglutinin disease are mild, but in those who have severe disease despite conservative measures, azathioprine, cyclosporine, or cyclophosphamide can be used. Rituximab is also useful. This is an anti-CD20 antibody. Steroids and splenectomy don't work well with cold agglutinin disease because the destruction occurs in the liver. You need to control the lymphocytes which control the production of IgM.

Hereditary Spherocytosis

Hereditary spherocytosis is a chronic mild hemolysis with spherocytes, jaundice, and splenomegaly from a defect in the red cell membrane. It is an autosomal dominant disorder where the loss of spectrin in the red cell membrane causes the red cell to form as a sphere, rather than as a more flexible and durable biconcave disc. Hemolysis occurs because the spheres are not able to pass the narrow passages in the spleen.

Clinical Presentation. A chronic disorder with mild to moderate symptoms of anemia. Because the hemolysis occurs in the spleen, there is often splenomegaly and jaundice. Severe anemia occasionally occurs from folate deficiency or Parvovirus B19 infection such as in sickle cell disease. Bilirubin stones often occur, leading to cholelithiasis, often at a young age.

Diagnosis. A normal to slightly decreased MCV anemia with the elevated LDH; indirect bilirubin and reticulocyte count similar to any kind of hemolysis. Although spherocytes may be present with autoimmune hemolysis, hereditary spherocytosis has a negative Coombs test. The cells have increased sensitivity to lysis in hypotonic solutions known as an osmotic fragility test. The mean corpuscular hemoglobin concentration (MCHC) is elevated.

Treatment. Most patients require no treatment beyond folate replacement chronically. In those with more severe anemia, removal of the spleen will eliminate the site of the hemolysis. The symptoms and jaundice will resolve but the spherocytes will remain.

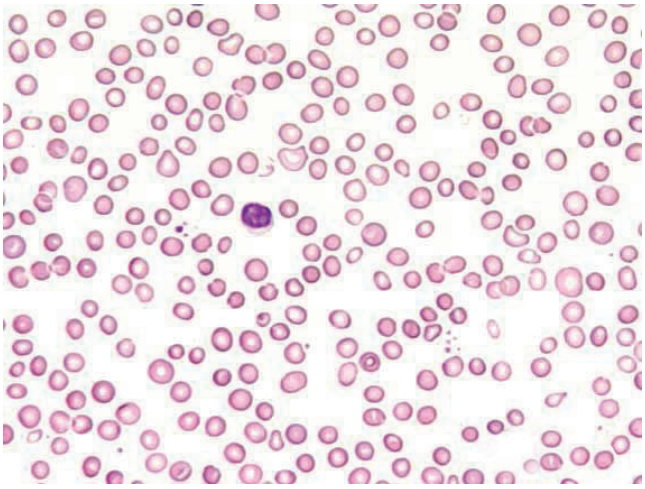


Figure 6-5. Features of Hereditary Spherocytosis Seen on Peripheral Blood Smear

Paroxysmal Nocturnal Hemoglobinuria

Note

Decay accelerating factor (DAF) is also known as CD55 and CD59. DAFs are the main proteins that protect RBCs from complement destruction.

Paroxysmal nocturnal hemoglobinuria (PNH) is a red cell membrane defect leading to intermittent dark urine and venous thrombosis and a chronic form of hemolysis. A red cell membrane defect in phosphatidyl-inositol glycan A (PIG-A) allows increased binding of complement to the red cell, leading to increased intravascular hemolysis. It is a clonal stem-cell disorder, and so can develop into aplastic anemia and leukemia. The cells are more susceptible to lysis by complement in an acid environment. Everyone becomes a little acidotic at night because of a relative hypoventilation.

PNH is often associated with bone marrow failure.

Clinical Presentation. In addition to symptoms of anemia, patients typically present with dark urine due to intravascular hemolysis. Thrombosis of major venous structures, particularly the hepatic vein (Budd-Chiari syndrome), is a common cause of death. The hemoglobinuria is most commonly in the first morning urine, since patients typically develop a mild acidosis at night.

Diagnosis. Besides the usual lab findings of hemolysis, such as an increased LDH, bilirubin, and reticulocyte count, these patients have brisk intravascular hemolysis and therefore have a low haptoglobin and hemoglobin in the urine. Hemosiderinuria occurs when the capacity of renal tubular cells to absorb and metabolize the hemoglobin is overwhelmed, and the sloughed off iron-laden cells are found in the urine. The gold standard test is flow cytometry for CD55 and CD59 on white and red cells. In PNH, levels are low or absent.

Treatment. Treatment for PNH depends on the severity of symptoms. Some patients with few or no symptoms require only folic acid and possible iron supplementation. Over time, the disease may progress and thus require more aggressive care.

- **For the anemic patient with signs of hemolysis**: prednisone to slow the rate of RBC destruction
- **For the patient with acute thrombosis**: thrombolytic therapy (streptokinase, urokinase, or tissue plasminogen activator), followed by long-term anticoagulation drugs to help prevent further blood clots
- Antiplatelet agents such as aspirin and ibuprofen to help prevent blood clots
- Antithymocyte globulin, but more often, red cell and/or platelet transfusions
- Allogeneic bone marrow transplantation (**mainstay of curative therapy**)
- New drug eculizumab (brand name Soliris) to treat symptoms of PNH (but still very expensive)

Avoid medications that increase the risk for thrombosis, such as oral birth control pills.

Note

Unfortunately, some patients will continue to develop blood clots despite aggressive anticoagulation agents.

Note

Although a new drug (eculizumab) has been approved by the FDA to treat symptoms of PNH, its high cost has limited its use.

Glucose-6-Phosphate Dehydrogenase Deficiency

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is a hereditary deficiency of an enzyme for producing the reducing capacity necessary for neutralizing oxidant stress to the red cell resulting in acute hemolysis.

Various forms of oxidant stress result in sudden hemolysis. The most common type of oxidant stress is actually from infections, not drugs. The most commonly implicated drugs are sulfa drugs, primaquine, dapsone, quinidine, and nitrofurantoin.

Clinical Presentation. Patients are normal until exposed to the stress. A sudden, severe, intravascular hemolysis can occur including jaundice, dark urine, weakness, and tachycardia. The history of recent drug ingestion is the main clue to the diagnosis.

Diagnosis. The usual findings of an intravascular hemolysis include high LDH, bilirubin, and reticulocyte count with a normal MCV, low haptoglobin, and hemoglobinuria. Heinz bodies are precipitated hemoglobin inclusions seen in red cells. Bite cells are seen on smear indicating the removal of the Heinz bodies. The definitive test is the G6PD level, which can be falsely normal immediately after an episode of hemolysis. Hence, the level is best tested about 1 week after the event.

Treatment. There is no specific therapy beyond hydration and transfusion if the hemolysis is severe. The main therapy is to avoid oxidant stress in the future.

Clinical Recall

Which of the following clinical scenarios is an indication for an exchange transfusion in a patient with sickle cell anemia?

A. Acute chest syndrome with a low hematocrit

B. Priapism with a normal hematocrit

C. Pneumococcal sepsis with an elevated hematocrit

D. Focal neurological deficits with an elevated hematocrit STEMI with a normal hematocrit

Answer: D

Aplastic Anemia

Aplastic anemia is failure of all 3 cell lines produced in the bone marrow, resulting in anemia, leukopenia, and thrombocytopenia (pancytopenia). The marrow is essentially empty with the absence of precursor cells.

Many things can cause bone marrow failure, but the most common cause of true aplastic anemia is not often determined. Causes include:

- Radiation, toxins such as benzene, drugs such as NSAIDs, chloramphenicol, alcohol, and chemotherapeutic alkylating agents
- Infections such as hepatitis, HIV, CMV, Epstein-Barr virus, or Parvovirus B19 in immunocompromised patients

Infiltration of the marrow with infections such as TB or cancer such as lymphoma can cause pancytopenia, but that is not truly aplastic anemia.

Clinical Presentation. Patients typically present with bleeding from the thrombocytopenia, and possibly with a combination of the findings associated with deficiencies in all 3 cell lines. Fatigue from anemia and infections from neutropenia may also occur. The clinical presentation may give a clue to the presence of pancytopenia but is not sufficient to determine a true aplastic anemia by clinical manifestations alone. The absence of a classical association such as benzene, radiation, or chloramphenicol would most certainly not exclude a diagnosis of aplastic anemia. The most common single etiology is idiopathic.

Diagnosis. Pancytopenia on a CBC is the first test. A bone marrow biopsy confirms the diagnosis when alternative etiologies for a pancytopenia are not present. In other words, the marrow is empty of almost all precursor cells as well as evidence of primary or metastatic cancer, infection, or fibrosis. The marrow is hypoplastic and fat filled with no abnormal cells seen.

Note

It is believed that T lymphocytes are primarily causal in the bone marrow failure, so drugs are used to decrease the T-cell response.

Treatment.

- Bone marrow transplant when patient is young/healthy and donor is available (cure rate nearly 90% for patients age <50)
- Immunosuppressive agents when bone marrow transplant not possible: combination antithymocyte globulin, cyclosporine, and prednisone (can lead to remission in 60–70% of patients)

LEUKEMIA

Leukemia is cancer of the blood and bone marrow. Acute leukemia involves the immature cells (stem cells), and chronic leukemia involves the mature cells.

Acute Leukemia

Acute leukemia is the rapid onset of bone marrow failure from the derangement of the pluripotent stem cell, causing the relentless destruction of the normal production of the entire bone marrow. Blood cells lose their ability to mature and function normally. Most cases arise with no apparent cause. However, there are several well known associations:

- Radiation exposure
- Benzene
- Chemotherapeutic agents such as melphalan and etoposide
- Some retroviruses
- Genetic disorders such as Down syndrome and Klinefelter
- Myelodysplasia and sideroblastic anemia

Clinical Presentation. Patients typically present with the effects of the leukemic blast cells crowding out the normal marrow cells, leading to symptoms of bone marrow failure (even if total WBC count is elevated or normal).

- Fatigue from anemia (**most common**)
- Bleeding from thrombocytopenia
- Infection from the underproduction or abnormal function of WBCs
- Enlargement of liver and lymph nodes
- Bone pain

Acute lymphocytic leukemia (ALL) is more common in children, and acute myelogenous leukemia (AML) is more common in adults, but they are indistinguishable clinically. ALL is more often associated with infiltration of other organs, but AML can do it as well. Disseminated intravascular coagulation (DIC) is associated with M3 promyelocytic leukemia. CNS involvement resembling meningitis is present at the time of initial diagnosis in a small number of patients (CNS involvement is most characteristic of M4 and M5 monocytic leukemia).

Rarely, a syndrome of "leukostasis" can occur when WBCs are extremely elevated. This results from sludging of the leukemic cell in the vasculature, and will cause headache, dyspnea, confusion, and possible brain hemorrhage. The leukostasis is due to a very high blast count; the blasts are very "sticky."

Diagnosis.

- CBC shows elevated WBC, thrombocytopenia and anemia
- Bone marrow biopsy showing >20% blasts (**confirms diagnosis**); the presence of blasts confirms acute leukemia but blast analysis cannot be relied upon to identify the type
  - AML is characterized by the presence of Auer rods, myeloperoxidase, and esterase. Auer rods are most specific for M3.
  - ALL is characterized by the presence of the common ALL antigen (CALLA) and terminal deoxynucleotidyl transferase (TdT).
- Hyperuricemia and increased LDH but those are nonspecific

Note

The acute leukemias do not result in splenomegaly.

Clinical Correlate

In about 10% of acute leukemias, depression of all 3 cell lines is evident (aleukemic leukemia). Many other disorders can present as pancytopenia similar to leukemia, i.e., aplastic anemia, infections involving the marrow, metastatic cancer involving the marrow, B12 deficiency, SLE, hypersplenism, and myelofibrosis.

None of these will have leukemic blasts circulating in the peripheral blood, however.

Ultimately, diagnosis rests upon the use of monoclonal antibodies, which recognize specific types of leukemia as well as the expression of specific CD antigens on the surfaces of the cells.

Treatment.

- Chemotherapy (all patients) to induce a remission
  - For AML: cytosine arabinoside (AraC) plus daunorubicin or idarubicin
  - For ALL: daunorubicin, vincristine, and prednisone
- Then, further rounds of chemotherapy to "consolidate" the leukemia
- For promyelocytic leukemia, add the vitamin A derivative all-trans-retinoic acid (ATRA)
- For leukostasis events, add leukapheresis to chemotherapy
- Later, adults with AML or ALL should be referred for allogeneic bone marrow transplantation

ALL patients must also undergo prophylaxis of the CNS to prevent relapse there; the best agent is intrathecal methotrexate.

Note

The FAB classification of the acute leukemias is often used but many centers are now using the WHO criteria, which focus on chromosomal changes that are identified. For example, ALL with 9,22 translocation (Philadelphia chromosome has a very bad prognosis).

For the exam, it is not needed to memorize these classifications.

Chronic Leukemia

Chronic Myelogenous Leukemia

Chronic myelogenous leukemia (CML) is a chronic myeloproliferative disorder characterized by the massive overproduction of myeloid cells. The cells retain most of their function until later in the course of the disease. Although the Philadelphia chromosome is characteristic of the disease, the cause of the production of this chromosome is unknown. It is a clonal disorder of myelocytes. The Philadelphia chromosome is a translocation between chromosomes 9 and 22, resulting in a gene producing an enzyme with tyrosine kinase activity.

Note

"Remission" means removal of over 99.9% of the leukemic cells in the body and the elimination of peripheral blasts in circulation.

Clinical Presentation. A markedly elevated WBC is found on routine blood count.

- Fatigue, night sweats, low-grade fever (**most common symptoms**)
- Abdominal pain from massive enlargement of the spleen (common)
- Bone pain from infiltration with WBCs
- Enlarged lymph nodes (rare)
- Infection and bleeding (rare, because the WBCs retain the majority of their function)

Note

CML can be confused with a leukemoid reaction. They are distinguishable based upon the leukocyte alkaline phosphatase score.

Diagnosis. The main feature of the disease is elevated WBCs, consisting predominantly of neutrophils with a left shift. Blasts are absent or present in very small amounts. The leukocyte alkaline phosphatase score (LAP) is diminished. Basophilia is characteristic of CML and *all* myeloproliferative disorders such as polycythemia vera. Although the B12 is often elevated, this would not be enough to establish the diagnosis. The Philadelphia chromosome is a far more specific test for CML and should be done in a patient with a markedly elevated white cell count. A low LAP score is not as important as the PCR for Bcr/Abl. The platelet count can also be markedly elevated.

Treatment.

- Imatinib (known by the brand name, Gleevec®), a direct inhibitor of the tyrosine kinase produced by the Philadelphia chromosome
  - Success rate nearly 90% (the milder the disease, the greater the degree of hematologic response)
  - Nearly 70% of patients may lose the Philadelphia chromosome
- Bone marrow transplantation if no response to imatinib

Chronic Lymphocytic Leukemia (CLL)

Chronic lymphocytic leukemia (CLL) is a massive overproduction of mature—but still leukemic—lymphocytes, usually from the monoclonal production of B lymphocytes. Etiology is unknown.

Clinical Presentation. CLL can often present as an asymptomatic elevation of WBCs found on routine blood count.

- Commonly older age (90% age >50)
- When symptoms are present, they are nonspecific: fatigue, lethargy, and uncomfortable enlargement of lymph nodes
- Infiltration of other parts of the reticuloendothelial system, i.e., spleen, liver, and bone marrow
- Infection and bleeding (rare)

CLL can be associated with various autoimmune phenomena such as thrombocytopenia and autoimmune hemolytic anemia.

Staging for CLL is as follows:

Stage 0: lymphocytosis alone
Stage 1: lymphadenopathy
Stage 2: splenomegaly
Stage 3: anemia
Stage 4: thrombocytopenia

Diagnosis. CLL is strongly suspected when an older patient has a marked elevation in WBCs with a marked lymphocytic predominance in the range of 80–98% lymphocytes. The marrow is often infiltrated with the leukemic lymphocytes. CD19 is an antigen strongly associated with CLL. Cell count is usually elevated (30,000–50,000, but may go as high as 150,000). "Smudge cells" seen on a smear are characteristic of CLL.

Treatment.

- **Early stage CLL with only elevated WBCs or enlarged lymph nodes**: no treatment
- **Advanced CLL with symptoms**: fludarabine (**drug of choice**), which is more effective than chlorambucil
- Autoimmune hemolysis and thrombocytopenia: prednisone
- Rituximab for patients who express CD20, especially with autoimmune ITP or hemolytic anemias
- Newer agents are now available for more select cases, e.g., bendamustine and ibrutinib.

Note

Bone marrow transplantation is no longer the clear first choice as treatment for CML. That is because of the extraordinary response to imatinib, as well as the high mortality associated with bone marrow transplant.

Note

Staging for CLL is important:

- **Survival of untreated stage 0 and 1 disease**: 10–12 years (even without treatment)
- **Survival of stage 3 and 4 disease**: 1–2 years

Note

A good **first-line therapy for CLL** is cyclophosphamide + fludarabine + rituximab.

Hairy cell leukemia (HCL), a subtype of CLL, is characterized by an accumulation of abnormal B lymphocytes. The malignant B lymphocytes ("hairy cells") accumulate in the bone marrow, interfering with the production of normal cells commonly causing pancytopenia.

HCL may be associated with repeated infections, often with unusual organisms as well as vasculitis.

Patients develop infections, anemia and fatigue, or easy bleeding. Early satiety may occur from massive splenomegaly.

- HCL is commonly considered in the differential diagnosis after routine blood count shows unexpectedly low numbers of cell lines or after unexplained bruising or recurrent infections in an otherwise apparently healthy patient.
- Bone marrow biopsy is necessary for final diagnosis: the biopsy is used to confirm both the presence of HCL and the absence of any additional diseases.
- Diagnosis can be confirmed by viewing the cells with a special stain known as TRAP (tartrate resistant acid phosphatase).
- Pancytopenia in HCL is caused primarily by marrow failure and splenomegaly. Bone marrow failure is caused by the accumulation of hairy cells and reticulin fibrosis in the bone marrow, as well as by the unfavorable effects of dysregulated cytokine production.
- For treatment, use the purine analogs cladribine (2CDA) or pentostatin (first-line). Almost all new patients will respond, with most experiencing a disease-free remission of 10+ years after taking one of these drugs just once. For cladribine-resistant disease, consider a monoclonal antibody (rituximab most common), which destroys the malignant B cells. Alpha interferon can stabilize the disease or produce a slow, minor improvement in 60% of patients.

Myelodysplastic Syndrome

Myelodysplastic syndrome (MDS) is an idiopathic disorder that is considered "pre-leukemic," in that a number of people go on to develop AML. The etiology is probably a genetic defect. The most common defect is 5q deletion or "5q–."

- Patients are commonly elderly
- Pancytopenia
- Elevated MCV
- Fatigue
- Infections
- Bleeding due to low cell counts
- Small number of blasts from 1–20%

Most patients die of infection or bleeding before they develop AML. This is because the disorder is slowly progressive and older patients "wear out" so to speak from cytopenias, more often than not going into the "blast phase" that characterizes AML. By definition, you must exclude B12 and folate deficiency because the disorder is so similar.

CBC and bone marrow are indispensable. You may find a bi-lobed neutrophil called a Pelger-Huet cell, which is characteristic. Genetic testing for the 5q– is essential.

Treatment is periodic transfusions and control of the infections as they arise. Disease-specific therapy consists of the TNF inhibitor lenalidomide or thalidomide. Azacitidine or decitabine is useful when the 5q- is present. Some patients who are young enough with a match can undergo bone marrow transplantation.

Note

It is the percentage of blasts present that tells how "close" a person with MDS is to developing AML.

Polycythemia Vera

Polycythemia vera is a disorder of RBC production. RBCs are produced in excessive amounts in the absence of hypoxia or increased erythropoietin.

Clinical Presentation.

- Markedly elevated hematocrit
- Splenomegaly
- Sometimes elevation of the platelet and white cell counts
- Thrombosis often in unusual locations such as the GI vessels
- "Plethora" or redness and fullness of the face
- Pruritis (40% of patients), particularly after exposure to warm water as in a shower, and possibly caused by abnormal histamine or prostaglandin production

Diagnosis. Diagnose with a high hematocrit in the absence of hypoxia, carbon monoxide poisoning, or elevated erythropoietin level. The most specific test is the Janus Kinase or JAK-2 mutation.

Treatment is phlebotomy. Hydroxyurea may be added or used as an alternative. Aspirin is used to reduce the risk of thrombotic events.

Recently, ruxolitinib, an inhibitor of kinases, has been used to treat severe cases of polycythemia not manageable with more conventional therapies. This same drug may be used in myelofibrosis with myeloid metaplasia.

Essential Thrombocythemia

Essential thrombocythemia is a type of platelet cancer. Platelet count may be over a million. There is either thrombosis or bleeding. The most specific test is JAK-2 mutation.

Treatment is hydroxyurea and sometimes anagrelide. The use of anagrelide is limited due to severe side effects.

Clinical Recall

Which of the following treatment options could be used in the management of stage 1 CLL?

A. Observation

B. Fludarabine

C. Prednisone

D. Rituximab

E. Fludarabine plus chlorambucil

Answer: A

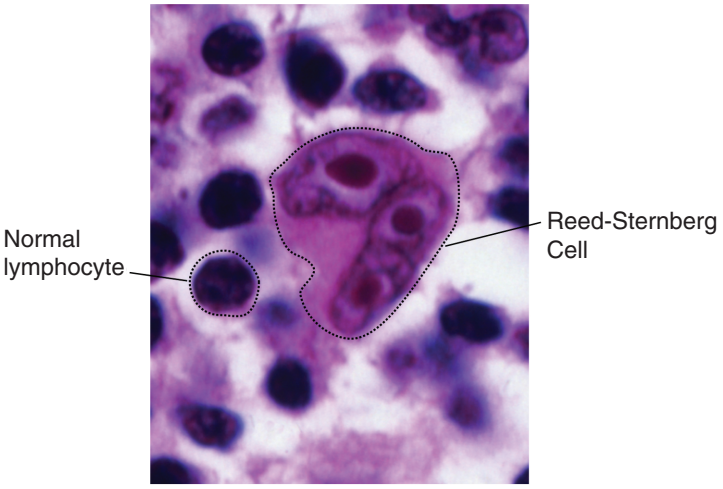
LYMPHOMA

Hodgkin Disease

A 32-year-old woman presents with a neck mass for the last several weeks. She also has fever, weight loss, and sweats.

Hodgkin disease is a neoplastic transformation of lymphocytes particularly in the lymph node. It is characterized by the presence of Reed-Sternberg cells on histology, which spreads in an orderly, centripetal fashion to contiguous areas of lymph nodes.

The disease most commonly presents age 20s or age 60s.



National Cancer Institute

Figure 6-6. Reed-Sternberg Cell

Although there is a clear increase in Hodgkin disease among relatives of those with the disease, there are no clear environmental or infectious etiologies for the disorder.

Clinical Presentation. Enlarged, painless, rubbery, nonerythematous, nontender lymph nodes are the hallmark of the disease. Patients may also develop what are labeled "B" symptoms, which are drenching night sweats, 10% weight loss, and fevers. Although pruritus is common in the disease, it is not one of the "B" symptoms. Cervical, supraclavicular, and axillary lymphadenopathy are the most common initial signs of disease. Lymphadenopathy may develop anywhere in the body, however. Extralymphatic sites such as splenic involvement, skin, gastric, lung, CNS, or any other organ may possibly be involved. Extralymphatic involvement is more common with non-Hodgkin lymphoma.

Staging is as follows:

Stage 1: one lymphatic group or single extra lymphatic site

Stage 2: two lymphatic groups or extra lymphatic sites on same side of the diaphragm

Stage 3: involvement of lymphatic groups on both sides of the diaphragm or involvement of any extralymphatic organ contiguous to the primary

Stage 4: widespread disease with involvement of diffuse extralymphatic sites such as bone marrow or liver

Staging is the same for both Hodgkin and non-Hodgkin lymphoma. In Hodgkin lymphoma, staging is the single most important predictor of outcomes.

Diagnosis.

- Excisional lymph node biopsy (essential first step)
- After diagnosis is made, determine the extent (stage) of disease
- Chest x-ray/CT, abdominal CT, or MRI will determine if the disease is localized to the supraclavicular area (bone marrow biopsy will definitively determine if disease is localized)
- CT scan is sensitive enough to detect any involved lymph nodes
- Size alone is insufficient to determine the content of some enlarged nodes. PET scan can also be used, in that it will stage the disease with accuracy. Further, it can be used to monitor for response and cure, and to determine the number of chemotherapy cycles that are required.
- Other labs tests that are often abnormal, but do not directly alter the stage of the disease, include the following:
  - CBC looking for anemia or increased WBC or platelets
  - Eosinophilia (common)
  - Elevated LDH indicates an adverse prognosis
  - ESR is useful prognostically
  - Elevated LFTs help determine the need for liver biopsy

Note

Adverse prognostic factors for Hodgkin include:

- Large mediastinal lymphadenopathy
- Age >40
- "B" symptoms
- Elevated ESR

Note

Lymphangiography and laparotomy are no longer routinely used for staging of Hodgkin.

Treatment.

- **Localized disease, i.e., stage IA and IIA**: radiation + adjunct chemotherapy
- **Evidence of "B" symptoms, and stage III-IV disease**: chemotherapy
  - Most effective combination chemotherapeutic regimen for Hodgkin disease is **ABVD** (adriamycin [doxorubicin], bleomycin, vinblastine, dacarbazine)
  - ABVD is superior to MOPP (mechlorethamine, [vincristine], prednisone, and procarbazine) in that it has fewer side effects, e.g., permanent sterility, secondary cancer formation, leukemia, aplastic anemia, and peripheral neuropathy

Hodgkin disease has several histologic subtypes. Lymphocyte-predominant has the best prognosis, and lymphocyte-depleted has the worst prognosis. The histologic subtype does not alter anything described. The lab tests, staging, and treatments are the same.

Non-Hodgkin Lymphoma

Non-Hodgkin lymphoma (NHL) is the neoplastic transformation of both the B and T cell lineages of lymphatic cells. It causes the accumulation of neoplastic cells in both the lymph nodes and (more often) diffusely in extralymphatic organs and the bloodstream. The Reed-Sternberg cell is absent.

Clinical Correlate

HIV and Epstein-Barr are more often associated with Burkitt lymphoma, and HIV is also associated with immunoblastic lymphoma—both high-grade lymphomas with an aggressive progression of disease.

There are a number of infectious and autoimmune disorders associated with NHL: hepatitis C, HIV, Epstein-Barr, HTLV-I, and *H. pylori*.

Clinical Presentation. Enlarged, painless, rubbery, nonerythematous, nontender lymph nodes are the hallmark of the disease. Patients may also develop what are labeled "B" symptoms, which are drenching night sweats, 10% weight loss, and fevers. Although pruritus is common in the disease, it is not one of the "B" symptoms. In this sense, NHL is the same as Hodgkin disease. The difference is that Hodgkin disease is localized to cervical and supraclavicular nodes 80–90% of the time, whereas NHL is localized only 10–20% of the time. NHL is far more likely to involve extralymphatic sites, as well as to have blood involvement similar to CLL. CNS involvement is also more common with NHL. HIV-positive patients often have CNS involvement.

Staging for NHL is the same as that for Hodgkin disease.

Diagnosis.

Note

Because the presence of marrow involvement in NHL means the patient has stage IV disease and will thus need combination chemotherapy, invasive testing such as the laparotomy is not needed.

- First, excisional lymph node biopsy
- Then, determine the stage of disease to identify appropriate therapy
- Although this is quite similar to that described for Hodgkin disease, there are important differences because **NHL is far more likely to be widespread at initial presentation**.
  - Lymphangiography is never necessary
  - Bone marrow biopsy is more central as an initial staging tool
  - Staging laparotomy is rarely needed
  - As with Hodgkin disease anemia, leukopenia, eosinophilia, high LDH, and high ESR often accompany the disease.
  - PET scan is highly sensitive and specific for nodal and extranodal sites but not for bone marrow disease.

Treatment.

- **Localized disease, i.e., stage IA and IIA**: radiation
- **Evidence of "B" symptoms and stages III and IV**: combination chemotherapy; the **preferred regimen** is CHOP (cyclophosphamide, hydroxy-adriamycin, vincristine, prednisone)
- **CNS lymphoma**: radiation + CHOP
- Relapses of NHL can be controlled with autologous bone marrow transplantation
- Some patients with NHL express CD20 antigen in greater amounts; for these patients, use monoclonal antibody rituximab, an anti-CD20 antibody
  - Adds survival benefit to the use of CHOP (thus, R-CHOP would then become first-line therapy)
  - Has limited toxicity
  - Can cause fulminant liver injury in those with active hepatitis B or C disease, so before using R-CHOP, test completely for hepatitis B and C

Tumor lysis syndrome

Tumor lysis syndrome (TLS) is an oncologic emergency caused by massive tumor cell lysis, with the release of large amounts of potassium, phosphate, and uric acid into the systemic circulation.

- Uric acid excretion can cause uric acid to build up in the renal tubules; it can also induce renal vasoconstriction, reduced renal blood flow, and inflammation, resulting in acute kidney injury.
- Hyperphosphatemia with calcium phosphate deposition in the renal tubules can also cause acute kidney injury.

TLS most often occurs after the initiation of cytotoxic therapy in patients with high-grade lymphoma (particularly Burkitt's and acute lymphoblastic leukemia), though it can occur spontaneously and with other tumor types having a high proliferative rate or large tumor burden.

- For patients about to receive chemotherapy for a cancer with a high cell turnover rate, e.g., lymphoma and leukemia, give prophylactic oral or IV allopurinol + IV hydration to maintain high urine output (>2.5 L/day)
- Rasburicase may be used as an alternative to allopurinol and is reserved for those at high-risk for developing TLS.

Alkalization of the urine as a treatment of TLS is controversial.

Note

Testing for hepatitis B is especially critical before starting rituximab therapy. If a patient is HBsAg-positive, then rituximab may be used cautiously as long as drugs to treat hepatitis B are also given (e.g., tenofovir).

Note

On the exam, you are not required to know the histologic subtypes of NHL or the specific chemotherapeutic regimens.

Clinical Recall

A 25-year-old man presents with enlarged, rubbery, non-erythematous, painless, non-tender cervical lymphadenopathy. He also admits to having weight loss, fever, and night sweats. What is the best initial diagnostic step?

A. Complete blood count with erythrocyte sedimentation rate

B. PPD or IFN-gamma release assay with CXR

C. Upper endoscopy with gastrointestinal biopsy

D. Excisional lymph node biopsy

E. Abdominal CT

Answer: D

PLASMA CELL DISORDERS

Multiple Myeloma

Multiple myeloma is a clonal abnormality of plasma cells resulting in their overproduction replacing the bone marrow, as well as the production of large quantities of functionless immunoglobulins. The disease is characterized by various systemic manifestations such as bone, kidney, and infectious complications. Etiology is unknown.

Clinical Pearl

Multiple myeloma causes a low anion gap.

Clinical Presentation. Bone pain is the most common clinical manifestation, usually in the back and the ribs, secondary to pathologic fractures. Radiculopathy from the compression of spinal nerve roots is also common. Infection particularly with encapsulated organisms such as *Pneumococcus* and *Haemophilus* is common. Renal failure and anemia are common. The symptoms of hypercalcemia such as polyuria, polydipsia, and altered mental status may occur. Weakness, fatigue, and pallor are common. Rarely, symptoms of a hyperviscosity syndrome such as blurry vision, confusion, and mucosal bleeding may occur.

Diagnosis. Although a normochromic, normocytic anemia is the most common laboratory finding, this is not specific for myeloma. A protein electrophoresis with a markedly elevated monoclonal immunoglobulin spike is present in almost all cases. This is most commonly IgG but may be IgA, IgD, or rarely a combination of two of these. In about 80% of individuals, routine x-ray will reveal the punched-out lytic lesion caused by the overproduction of osteoclast activating factor from the plasma cells and/or pathologic fractures at the time of diagnosis. Most commonly involved are the vertebrae, ribs, pelvic bones, and bones of the thigh and upper arm. If multiple myeloma is suspected with normal x-ray, consider MRI, CT, or PET. Serum B2 microglobulin is elevated in 75% of patients, as is the production of IL-6. Hypercalcemia from the destruction of bone is common, as is an elevation in the BUN and creatinine from the damage to the kidney from the immunoglobulins, Bence-Jones protein, calcium, and hyperuricemia. A bone marrow biopsy with >10% plasma cells confirms a diagnosis of multiple myeloma. Bence-Jones protein is often not detected by a standard protein test on a urinalysis, which mainly is meant to detect albumin. A specific test for Bence-Jones protein involving acidification of the urine is required. Increased gamma globulin levels will increase the total protein and decrease the albumin level.

Treatment.

- **Patients age <70**: autologous bone marrow transplantation in an attempt to cure the disease
- **Patients age >70**: melphalan and prednisone
- **Candidates for transplant**: thalidomide (or lenalidomide) and dexamethasone
- Non-candidates for transplant: melphalan, prednisone, and thalidomide
- Hydration and loop diuretics first, and then IV bisphosphonates, e.g., zoledronic acid to reduce bone pain and pathologic fractures
- Bortezomib, a proteasome inhibitor, is useful for relapsed myeloma or as an addition to the other medications; it can be combined with steroids, melphalan, or lenalidomide (thalidomide)

Monoclonal Gammopathy of Uncertain Significance (MGUS)

MGUS is the overproduction of a particular immunoglobulin by plasma cells, without the systemic manifestations of myeloma such as bone lesions, renal failure, anemia, and hypercalcemia. It is a very common abnormality, seen in 1% of all patients age >50 and 3% of patients age >70.

The cause of MGUS is unknown. Some patients with this condition may progress to multiple myeloma.

Clinical Presentation. Patients are asymptomatic. The condition is found on routine blood testing.

Diagnosis.

- Elevated monoclonal immunoglobulin spike of serum protein electrophoresis (SPEP) in amounts lower than those seen in myeloma
- Normal creatinine, calcium, and hemoglobin
- Elevated total serum protein (**clue to diagnosis**)
- No lytic bone lesions; bone marrow has <10% plasma cells
- Normal beta-2 microglobulin level in most patients

Treatment is neither effective nor necessary, but monitor carefully.

PLATELET DISORDERS

Immune Thrombocytopenic Purpura

Immune thrombocytopenic purpura (ITP) is the idiopathic production of an antibody to the platelet, leading to removal of platelets from the peripheral circulation by phagocytosis by macrophages. The platelets are bound by the macrophage and brought to the spleen, leading to low platelet count.

ITP is often associated with lymphoma, CLL, HIV, connective tissue diseases, and *H. pylori*, but it may be idiopathic.

Note

The level of B2 microglobulin may be predictive of outcome. A higher level is associated with a poorer outcome.

Clinical Presentation. Like all platelet disorders, initial symptoms include signs of bleeding from superficial areas of the body, e.g., the skin, nasal/oral mucosa, GI tract, urine, and vagina. Women > men, and patients are otherwise healthy.

- Commonly young age
- Epistaxis
- Bruising
- Hematuria
- Dysfunctional uterine bleeding and possible GI bleeding
- Petechiae, purpura, and ecchymoses (common)
- Splenomegaly is absent

Diagnosis.

- Thrombocytopenia (**major finding**)
- Normal spleen on exam and on imaging (**characteristic**)
- Antiplatelet antibodies have a high sensitivity but poor specificity
- Bone marrow should be filled with megakaryocytes, indicating that there is a problem with platelet destruction and not platelet production. The bone marrow will also exclude other causes of thrombocytopenia such as primary or metastatic cancer, infiltration by infections such as TB or fungi, or decreased production problems such as drug, radiation, or chemotherapy effect on the bone marrow.
- Large platelets will be round on peripheral smear
- High MPV (mean platelet volume), indicating a high overall platelet volume (and correlating with younger platelets, which are bigger)
- Normal peripheral smear and creatinine, excluding other platelet destruction problems such as HUS, TTP, and DIC

Treatment.

- Prednisone (**first-line**) for almost all patients
- If no response to repeated steroids and platelets continue to be very low (<10,000–20,000/mm^3), consider splenectomy
- If no response to splenectomy, use thrombopoietin agents romiplostim or eltrombopag (rituximab is an alternative)
- For profoundly low platelet counts (<10,000/mm^3) or patients at risk for life-threatening bleeding, use IVIG or RhoGAM™ (equally effective but RhoGAM can only be used in Rh-positive patients)

Clinical Pearl

Platelet disorders can broadly be classified into 2 groups:

- Quantitative (low platelet count, eg, ITP)
- Qualitative (normal platelet count but abnormal platelet function, eg, von Willebrand, Bernard Soulier)

Note

Today, bone marrow examination is rarely done to diagnose ITP. Because the megakaryocytes are normal or high, the platelets that are present will be younger (thus, larger and more functional), i.e., the large platelets work better. Hence bleeding is less common in ITP than it used to be.

Von Willebrand Disease (vWD)

A 22-year-old woman comes to the ED with epistaxis and heavy periods. Her PT is 11 seconds (normal), PTT 40 seconds (prolonged), and platelets 217,000/mm^3.

vWD (**most common congenital disorder of hemostasis**) is an autosomal dominant disorder leading to decreased amounts of von Willebrand factor. As a result of the decreased von Willebrand factor, there is an increased predisposition to platelet-type bleeding.

vWD also results in a decreased ability of platelets to adhere to the endothelial lining of blood vessels. This is different from platelets aggregating with each other, which is mediated by fibrinogen. In vWD, aggregation is normal, whereas adherence is abnormal.

Clinical Presentation. Patients with vWD manifest platelet-type bleeding such as that described for ITP. This is mucosal and skin bleeding such as epistaxis, petechiae, bruising, and menstrual abnormalities. Both platelet problems as well as clotting factor abnormalities can result in GI and urinary tract bleeding. There is often a marked increase in bleeding after the use of aspirin.

Diagnosis.

- Normal platelet count and appearance
- Increased bleeding time, especially after the use of aspirin
- Low level of von Willebrand factor (or factor VIII antigen)
- Abnormal ristocetin platelet aggregation test (which examines the ability of platelets to bind to an artificial endothelial surface [ristocetin])
- Elevated PTT (some patients) because of a concomitant decrease in levels of factor VIII coagulant portion

Treatment.

- Mild bleeding or for minor surgical procedures: desmopressin acetate (DDAVP) to release subendothelial stores of von Willebrand factor
- If no response with desmopressin: factor VIII replacement, which contains von Willebrand factor (replaces the use of cryoprecipitate, which is now seldom necessary)
- Fresh frozen plasma (FFP) is not useful.
- Patients should avoid aspirin.

Clinical Correlate

In an autosomal dominant disorder, the mutated gene is a dominant gene located on a nonsex chromosome (autosome). Only one mutated copy of the autosomal gene is needed to cause disease.

Note

For the exam, you will not need to know the various subtypes of vWD.

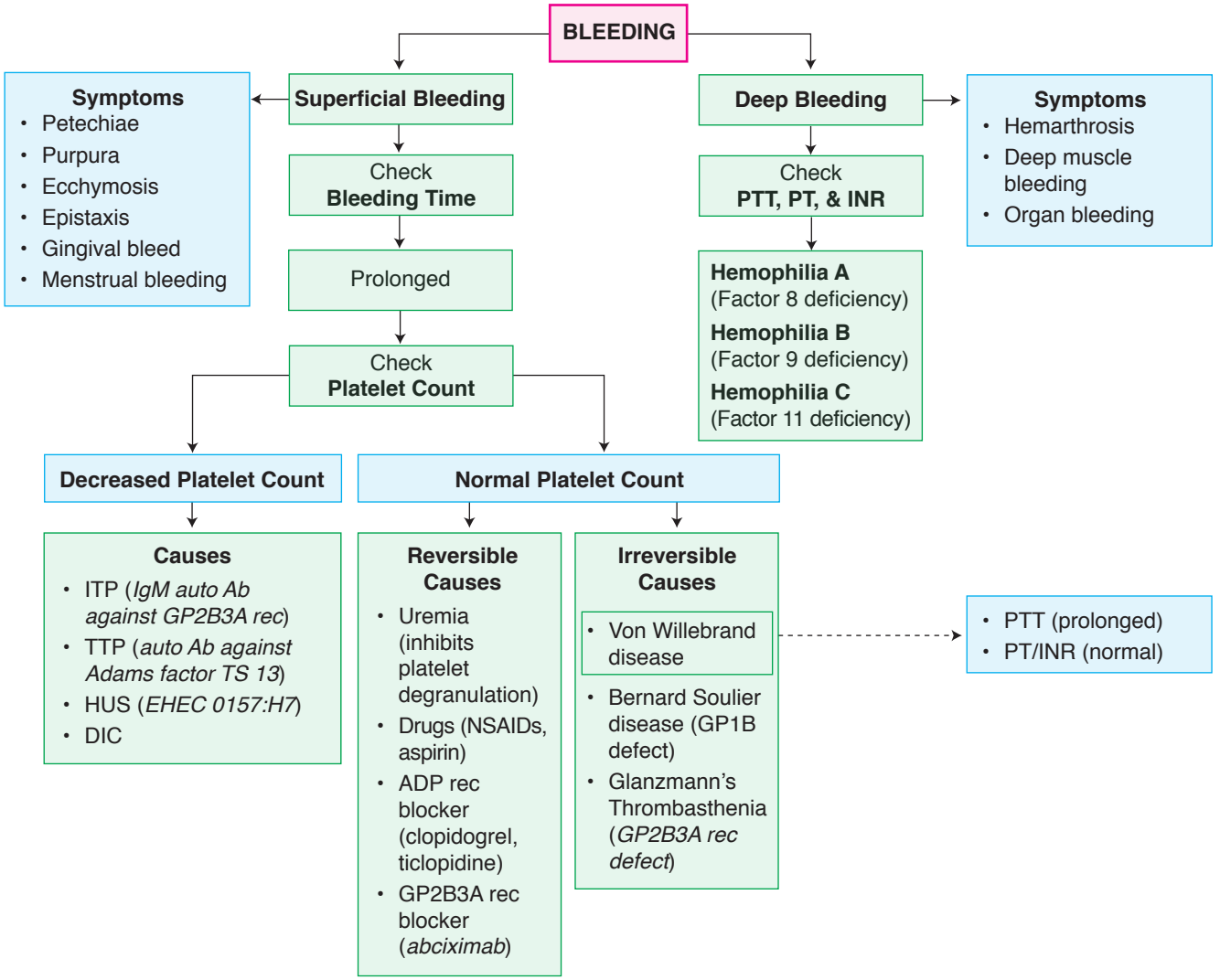


Figure 6-7. Evaluation of Patients with Bleeding

Clinical Correlate

Hemophilia A and B are both X-linked recessive disorders. Males have disease, while females are carriers.

COAGULOPATHY

Hemophilia A and B

Hemophilia A is a deficiency of clotting protein factor VIII, while **hemophilia B** is a deficiency in clotting protein factor IX. Both conditions result in an increased risk of bleeding.

Hemophilia A is far more common than B.

Clinical Presentation.

- **Mild deficiencies** (25% or greater activity): asymptomatic or symptomatic only with surgical procedures or trauma
- **More severe deficiencies** (<5–10% activity): spontaneous bleeding
  - Factor-type bleeding is generally deeper than bleeding from platelet disorders
  - Factor-type bleeds include hemarthrosis, hematoma, GI bleeding, and urinary bleeding
  - Bruising and CNS bleeding can also occur
- Severe hemophilia is obvious in most patients by age 2. The disorder becomes apparent often at the time of circumcision.

Diagnosis. A prolonged PTT with a normal PT is expected. A factor deficiency is strongly suspected when a 50:50 mixture of the patient's blood is created with a normal control and the PTT drops to normal (known as a "mixing study").

If PTT does not correct with mixing, then an antibody inhibitor of the factor is suspected. The next step is to identify the specific factor that is deficient. Proceed with testing of factor VIII and IX levels to get a precise diagnosis.

Treatment.

- **Mild hemophilia**: desmopressin (works by releasing subendothelial stores of factor VIII)
  - Desmopressin can also be used prior to surgical procedures in mild hemophiliacs.
  - Desmopressin does not work for hemophilia B.
- **Severe hemophilia**: replacement of the specific factor (cryoprecipitate and FFP rarely used)

Clinical Correlate

Females do not express hemophilia because they would have to be homozygous, which is a condition resulting in intrauterine death of the fetus.

Note

With diagnosis of hemophilia, the mixing study will only confirm a deficiency; it will not identify the specific factor. Factor VIII or IX levels are needed for a precise diagnosis.

Table 6-3. Causes of Prolonged PT or PTT

	Prolonged PT	Prolonged PTT	Prolonged PT and PTT
Inherited causes	Factor VII deficiency	vWF and factors VIII, IX, XI, or XII deficiencies	Prothrombin, fibrinogen, factor V, factor X, or combined factor deficiencies
Acquired causes	• Vitamin K deficiency • Liver disease • Warfarin use • Factor VII inhibitor	• Heparin • Antiphospholipid antibody	• Vitamin K deficiency • Liver disease • Disseminated intravascular coagulation • Supratherapeutic heparin or warfarin • Combined heparin and warfarin use • Direct thrombin inhibitors • Inhibitor of prothrombin, fibrinogen, or factor V or X

PT, prothrombin time; PTT, partial thromboplastin time; vWF, von Willebrand factor.

Vitamin K Deficiency

Vitamin K deficiency can lead to decreased production of factors II, VII, IX, and X.

It can result from dietary deficiency, malabsorption, or antibiotics, which kill the bacteria in the colon that produce vitamin K (most commonly broad-spectrum drugs such as fluoroquinolones, cephalosporins, and other penicillin derivatives).

Clinical Presentation. Bleeding may mimic that of hemophilia and may occur at any site. Look for oozing at venipuncture sites.

Diagnosis. Both the PT and PTT are elevated. The PT usually elevates first and more severely.

Correcting the PT and PTT in response to giving vitamin K is the most common way to confirm diagnosis.

Treatment.

- **Severe deficiency and bleeding**: infusions of FFP + parenteral vitamin K replacement to correct the underlying production defect
- **Mild deficiency**: oral vitamin K replacement (very effective and easy to use)

Liver Disease

Clinical Correlate

With liver disease, **factor VII levels** are the first to be depleted.

Liver disease can be caused by coagulopathy due to decreased production of clotting factors by the liver. Any severe liver disease or cirrhosis will lead to decreased production of the majority of clotting factors that are generally all made in the liver—except for factor VIII and von Willebrand factor. The first factor to be depleted is factor VII.

Clinical Presentation. Bleeding may occur at any site, but the GI tract is the most common site.

The disorder is clinically indistinguishable from vitamin K deficiency except that there is no improvement when vitamin K is given.

Diagnosis.

- Elevated PT and PTT, but PT elevates first and is often more severely affected
- Clear history of liver disease (common), suggesting the diagnosis; low platelets are also common as a result of the hypersplenism that accompanies the liver disease

Treatment. For acute situations such as severe bleeding, e.g., melena, FFP is used. For long-term management, evaluate the nature of the liver disease.

Disseminated Intravascular Coagulation

DIC is consumptive coagulopathy from major underlying illness, resulting in the consumption of both platelet and clotting factor type and occasionally thrombosis. The bleeding is associated with a marked production of fibrin degradation products such as d-dimers.

Although DIC is essentially an idiopathic disorder, there is almost always a major underlying disease in the case history.

- Evidence of sepsis (**most common**); gram-negative sepsis causes DIC by the releasing endotoxin
- Rhabdomyolysis
- Adenocarcinoma
- Heatstroke
- Hemolysis from transfusion reactions
- Burns

- Head trauma
- Obstetrical disasters such as abruptio placenta and amniotic fluid embolism
- Pancreatitis
- Snakebite

Promyelocytic leukemia (M3) is a classic association with DIC. In the acute form, the destruction of leukemic granulocyte precursors causes large amounts of proteolytic enzymes to release from their storage granules, resulting in microvascular damage.

Other malignancies may also cause DIC by augmenting the expression of various oncogenes that result in the release of tissue factor.

DIC can be acute or chronic.

- **Acute DIC** develops when sudden exposure of blood to procoagulants (tissue factor, tissue thromboplastin) generates intravascular coagulation. The compensatory hemostatic mechanisms are quickly overwhelmed, and, as a consequence, a severe consumptive coagulopathy leading to hemorrhage develops.
- **Chronic DIC** reflects a compensated state that develops when blood is continuously or intermittently exposed to small amounts of tissue factor. Compensatory mechanisms are not overwhelmed. Chronic DIC is more frequently observed in patients with solid tumors and in those with large aortic aneurysms.

Clinical Presentation. Bleeding from any site in the body is possible because of a decrease in both the platelet as well as clotting factor levels. Thrombosis is less common. Hemolysis is often present and may lead to acute renal failure, jaundice, and confusion.

Diagnosis. DIC is suspected when a patient has a serious underlying disorder as described with bleeding and there is elevation in both the PT and PTT with a decrease in the platelet count. The fibrinogen level is often low because it has been consumed. D-dimers and fibrin-split products are present in increased amounts, suggesting the consumption of all available elements of the coagulation system. The peripheral blood smear often shows the schistocytes as fragmented cells consistent with intravascular hemolysis.

Treatment. Because most patients present with severe bleeding, FFP and sometimes platelet transfusions are necessary to correct the bleeding. Heparin is controversial and is rarely used, except in those patients presenting predominantly with thrombosis. Don't forget to correct the underlying disorder.

Thrombotic Thrombocytopenic Purpura/Hemolytic Uremic Syndrome

Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) are varieties of the same disease, with considerable overlap. There is no specific diagnostic test, so the diagnosis is based on the clinical triad (HUS) or pentad (TTP).

- Most cases of TTP are idiopathic and arise from inhibition of the enzyme ADAMTS13, which is responsible for cleaving large multimers of von Willebrand factor into smaller units. The increase in circulating multimers of vWF increase platelet adhesion to areas of endothelial injury, particularly the arteriole-capillary junctions.
- Some cases of TTP are associated with specific diseases (cancer, HIV) and drugs (ticlopidine, clopidogrel, cyclosporine, and interferon) and are referred to as secondary TTP. ADAMTS13 activity is generally not as depressed in secondary TTP.

HUS predominantly affects children. Most cases are caused by a shiga-like toxin produced by *E. coli* O157:H7, although *Campylobacter*, *Shigella,* and some viruses have also been implicated. It is one of the most common causes of acute renal failure in childhood and carries up to 10% mortality.

HUS consists of a triad of hemolytic anemia, uremia, and thrombocytopenia. TTP has the same 3 findings, and is also associated with fever and neurologic problems. You do not have to have all 5 findings simultaneously to be considered to have TTP. The anemia in both will be intravascular in nature and will have an abnormal blood smear showing schistocytes, helmet cells, and fragmented red cells. LDH and reticulocyte count will be elevated and haptoglobin decreased.

Treatment.

- **TTP**: plasmapheresis (for very severe cases, add rituximab)
- **HUS**: plasmapheresis for severe cases only; mild disease resolves spontaneously
- Do not give antibiotics to those with possible HUS (organism may release more toxins as it dies and may worsen the disease).
- Do not transfuse platelets, even if platelet count is low (can worsen the CNS and renal abnormalities by giving more platelets as a substrate to precipitate; small platelet plugs are actually the cause of the problem).

Heparin-Induced Thrombocytopenia

Heparin-induced thrombocytopenia (HIT), a complication of heparin therapy, can occur with any form of heparin. It is more common with IV unfractionated heparin than with low molecular weight (LMW) heparin.

Type 1 HIT presents within first 2 days after exposure to heparin.

- Non-immune-mediated disorder that results from the direct effect of heparin on platelet activation
- This form of thrombocytopenia is benign, self-limited, and not associated with bleeding or increased risk of thrombosis

Type 2 HIT (**generally referenced as HIT**) occurs 4-10 days after exposure to heparin.

- Immune-mediated disorder
- Has life- and limb-threatening thrombotic complications (low platelet count causes thrombosis)

Note

Because the most common complications of HIT are venous thromboembolism and arterial thrombosis, it is sometimes called **heparin-induced thrombocytopenia and thrombosis**.

Suspect HIT when a patient who is receiving heparin has a decreased platelets, particularly if the drop is >50% of the baseline count, even if the platelet count nadir remains >150,000.

Clinically, HIT is not often marked by bleeding; the most common complication is venous thromboembolism (deep venous thrombosis, pulmonary embolism), and less often, arterial thrombosis (stroke, myocardial infarction). Thrombosis develops in approximately 20% of patients with HIT, with mortality as high as 30%.

Diagnosis of HIT is based on the combined clinical findings, thrombocytopenia characteristics, and lab studies of HIT antibodies (positive in ~85% of patients with type 2 HIT).

Treatment.

- Discontinue all heparin products (including heparin flushes of IV catheters)
- Replace with an alternative anticoagulant such as argatroban or fondaparinux (parenteral factor X inhibitor)

Patients diagnosed with HIT should avoid all forms of heparin for life.

Warfarin

Warfarin is the most widely prescribed anticoagulant for the prevention and treatment of thromboembolic disease. It was initially introduced as a pesticide against rodents, and long-acting forms of warfarin are still used for this purpose.

Warfarin anticoagulates by inhibiting an enzyme that recycles oxidized vitamin K to its reduced form. Warfarin does not antagonize the action of vitamin K, but rather antagonizes vitamin K recycling. Once vitamin K is reduced, the vitamin K dependent factors (factors 2,7,9,10) are eventually reduced (3-5 days).

Despite its efficacy, treatment with warfarin has several limitations.

- Many commonly used medications interact with warfarin, as do some foods—particularly green vegetables—since they typically contain large amounts of vitamin K.
- Warfarin activity has to be monitored by the PT and international normalized ratio (INR) to ensure an adequate yet safe dose (typically **INR 2–3** is considered adequate and safe anticoagulation). The pharmacologic action of warfarin may always be reversed by fresh vitamin K.

Table 6-4. Recommended Management of a Supratherapeutic INR

INR	Bleeding Present	Recommended Action
<Ther to 5.0	No	• Lower warfarin dose, **or** • Omit a dose and resume warfarin at a lower dose when INR is in therapeutic range, **or** • No dose reduction needed if INR is minimally prolonged
>5.0 to 9.0	No	• Omit the next 1–2 doses of warfarin, monitor INR more frequently, and resume treatment at a lower dose when INR is in therapeutic range, **or** • Omit a dose and administer 1–2.5 mg oral vitamin K*
>9.0	No	• Hold warfarin and administer 5–10 oral vitamin K. Monitor INR more frequently and administer more vitamin K as needed. Resume warfarin at a lower dose when INR is in therapeutic range.
>20	—	• Hold warfarin and administer 10 mg vitamin K by slow IV infusion; supplement with FFP, or recombinant human factor VIIa, depending on clinical urgency. Monitor and repeat as needed.
Any	Life-threatening	As per "INR >20" above

Ther: therapeutic INR range for the patient in question INR

*Preferred in patients at increased risk for bleeding (e.g., history of bleeding, stroke, anemia).

Clinical Recall

What is the most appropriate step in the management of a patient with heparin-induced thrombocytopenia and thrombosis?

A. Continue heparin and administer warfarin

B. Discontinue heparin and administer argatroban

C. Discontinue the heparin substitute with warfarin

D. Continue heparin and add lepirudin

E. Continue heparin and monitor closely

Answer: B

Infectious Diseases 7

Learning Objectives

- ❑ Provide an overview of common antibiotics and their uses
- ❑ Describe the unique conditions and considerations for infections which occur in the CNS, head, neck, lung, pericardium, endocardium, GI tract, urinary tract, bones, and joints
- ❑ Present the treatment of acute herpes viral hepatic infections
- ❑ Describe the diagnosis and management of Lyme disease and Rocky Mountain spotted fever
- ❑ Describe the epidemiology, presentation, and treatment of genital/sexually transmitted diseases and AIDS

ANTIBIOTICS

Antibiotics can be grouped by their chemical class or by the type of organism they are effective against.

The organisms that cause specific diseases do not change much over time. For example, MRSA, *Staphylococcus aureus* is still the most common cause of osteomyelitis, and *Escherichia coli* is still the most common cause of pyelonephritis.

What does change over time is the antibiotic that is effective against each organism and the sensitivity pattern of each organism.

Gram-Positive Cocci

Semisynthetic penicillinase-resistant penicillins

Staphylococcal and streptococcal organisms are effectively treated by medications such as the semisynthetic penicillins, including oxacillin, cloxacillin, dicloxacillin, and nafcillin. These agents are exclusively effective against gram-positive cocci, in particular staphylococci.

Note

In March 2020, the WHO declared a global pandemic of a new coronavirus, **COVID-19**. This topic is **unlikely to be on the USMLE this year**, but preliminary research shows the following:

- ssRNA enveloped coronavirus transmitted via droplets to the lungs
- Highly contagious and likely a zoonotic infection (bats)
- Incubation time 4–14 days
- **Can be spread by asymptomatic carriers**

Note

Do not use vancomycin if the organism is oxacillin-sensitive.

Note

- **Methicillin** was one of the original drugs in this class. However, it may cause interstitial nephritis and so is not used clinically. Thus, the term "methicillin-sensitive" or "methicillin-resistant *Staphylococcus aureus* (**MRSA**)" is a misnomer because methicillin is not actually used.
- When the term MRSA is used, think of oxacillin, cloxacillin, dicloxacillin, and nafcillin.

Note

On the exam, your answers should correspond most specifically to the organism you are treating. If you are treating a sensitive *Staph aureus* or *Strep*, answer with a specific gram-positive drug. Do not give an answer which provides more coverage than needed, unless there is evidence to support the presence of other organisms. If you are treating a gram-positive infection, answer with a first-generation agent.

When *Staphylococcus* is sensitive to the semisynthetic penicillins, and concurrent gram-negative infection is not suspected, these are the ideal agents. They are more effective than vancomycin when the organism is sensitive. These drugs are also sometimes referred to as "beta-lactamase-resistant penicillins" or "antistaphylococcal penicillins." Nevertheless, the latter term is somewhat misleading because they are also effective against a number of streptococci, such as *S. pneumoniae*, the Viridans group, and groups A, B, C, and G Strep.

Penicillin G, penicillin VK, ampicillin, and amoxicillin

These agents are effective against streptococci, such as *S. pyogenes*, viridans group streptococci, and *S. pneumonia*, but not against staphylococci.

- Ampicillin and amoxicillin are effective against staph only when **ampicillin is combined with the beta-lactamase inhibitor sulbactam** or when **amoxicillin is combined with clavulanate**.
- Ampicillin has some activity against *E. coli*.
- Both ampicillin and amoxicillin are effective against enterococci and *Listeria*.
- Penicillin is effective against *Actinomyces* (think of this with dental abscess in someone with periodontal disease).

Cephalosporins

The first- and second-generation cephalosporins all cover the same range of organisms that the semisynthetic penicillins cover, i.e., staphylococci and streptococci, plus some gram-negative organisms.

- First-generation agents (**cefazolin, cefadroxil, cephalexin**) only reliably cover *E. coli*, *Proteus mirabilis*, and *K. pneumoniae*; cefazolin has been proven more effective for MSSA than nafcillin or oxacillin.
- Second-generation agents (**cefoxitin, cefotetan, cefuroxime, cefprozil, loracarbef**) will cover everything a first-generation cephalosporin covers, as well as a few more gram-negative bacilli such as *Providencia*, *Haemophilus*, *Klebsiella*, *Citrobacter*, *Morganella*, and *Proteus*.
- Third-generation agents, particularly ceftazidime, are not reliable in their staphylococcal coverage.
- Fourth-generation cephalosporins such as cefepime will cover staph and strep, although this should never be the answer when the infection is exclusively gram-positive.

For those with allergy to penicillin, there is only a <1% risk of cross-reaction with cephalosporins. When this reaction occurs it is seldom an anaphylactic reaction.

- When the allergic reaction is described as a rash, a cephalosporin can safely be used.
- When the allergic reaction is severe, e.g. anaphylaxis, a cephalosporin should not be used.
- For minor infections, use a macrolide (clarithromycin or azithromycin) or one of the new fluoroquinolones (levofloxacin, gemifloxacin, or moxifloxacin).
- For serious infections in those with a life-threatening penicillin allergy, use vancomycin, linezolid, or daptomycin.

Macrolides, fluoroquinolones, and clindamycin

For gram-positive infections, macrolides (erythromycin, clarithromycin, azithromycin), fluoroquinolones (levofloxacin, gemifloxacin, moxifloxacin), and clindamycin are alternatives to penicillins and cephalosporins. Macrolides should not be used for serious staph infection.

The respiratory quinolones are very good for streptococcal infections, particularly *Strep pneumoniae*, especially in penicillin-resistance. They are also sufficient against staph. Ciprofloxacin is a quinolone as well, but it does not cover *Strep pneumoniae*. Ciprofloxacin has no gram-positive coverage.

Vancomycin, linezolid, tigecycline, ceftaroline, telavancin

For gram-positive infections, vancomycin (side effects include thrombocytopenia; do not use if MIC >2), linezolid (side effects include thrombocytopenia and lactic acidosis; do not use with SSRIs), and tigecycline are effective. Alternatives include ceftaroline, telavancin, daptomycin (monitor CPK; do not use for pneumonia; neutralized by surfactant). Other options are dalbavancin (2 doses one week apart, via IV) and oritavancin (one dose via IV).

When there is a life-threatening penicillin-allergy or MRSA, use the listed agents (vancomycin is preferred for MRSA).

Ceftaroline is used like a third-generation cephalosporin, such as ceftriaxone, combined with a MRSA agent, such as vancomycin. Ceftaroline is the only cephalosporin to cover MRSA. These medications should not be used if the organism is sensitive to methicillin.

Note

Daptomycin, ceftaroline, and tigecycline are also effective against MRSA.

Note

Quinupristin/dalfopristin is no longer used.

Gram-Negative Bacilli

Penicillins

Penicillins (piperacillin, ticarcillin, mezlocillin) are fully active against the full range of gram-negative bacilli, such as *Pseudomonas*, as well as the Enterobacteriaceae. Enterobacteriaceae include *E. coli*, Proteus, *Enterobacter, Citrobacter, Morganella, Serratia*, and *Klebsiella*. They are **only active against staph when combined with a beta-lactamase inhibitor** such as piperacillin/tazobactam or ticarcillin/clavulanate. Ampicillin/sulbactam and amoxicillin/clavulanate will also cover staph and gram-negative bacilli, but not *Pseudomonas*.

All penicillins will cover sensitive streptococci, but if the patient has only a sensitive strep, give a narrower agent, such as penicillin G or penicillin VK.

Cephalosporins

Third- and fourth-generation agents (ceftazidime; cefotaxime; ceftriaxone, and cefepime) are fully active against the full range of gram-negative bacilli, such as the Enterobacteriaceae.

- Only ceftazidime and cefepime cover *Pseudomonas.*
- Cefepime also covers staph.
- Side effects of ceftriaxone include biliary/gallbladder sludge and autoimmune hemolytic anemia.

Second-generation agents cover some of the Enterobacteriaceae, but not *Pseudomonas*. Although predominantly for use against gram-negative organisms, ceftriaxone and cefotaxime are the best answers for penicillin-insensitive pneumococci-causing meningitis or pneumonia.

Note

Cephalosporins are safe in penicillin allergy if it is only a rash.

Clinical Pearl

Ceftriaxone does not have adequate pseudomonal coverage.

Quinolones

Quinolones (ciprofloxacin, levofloxacin, delafloxacin, moxifloxacin, ofloxacin) cover most of the Enterobacteriaceae, such as *E. coli, Proteus, Enterobacter, Haemophilus, Moraxella, Citrobacter, Morganella, Serratia,* and *Klebsiella*. Only ciprofloxacin reliably covers *Pseudomonas*.

The respiratory fluoroquinolones (moxifloxacin, levofloxacin, and gemifloxacin) are also active against gram-positive cocci, in particular *Strep pneumoniae*. They are among the first-line therapies for empiric treatment of pneumonia because they will also cover *Mycoplasma*, *Chlamydia*, and *Legionella*.

Ciprofloxacin does not cover gram-positives and cannot be used for pneumonia or cellulitis.

Note

The FDA has recently issued a warning to avoid using fluoroquinolones because of severe side effects–tendonitis, tendon rupture, peripheral neuropathy. These medications can also cause QT prolongation.

Aminoglycosides and monobactams

Aminoglycosides (gentamicin, tobramycin, amikacin) and monobactams (aztreonam) have essentially the same gram-negative coverage as listed for the other agents. Although aminoglycosides can be synergistic with a penicillin in the treatment of staph, they are essentially exclusively gram-negative agents. Aztreonam is exclusively a gram-negative agent, with no strep or staph coverage at all.

Carbapenems

Carbapenems (imipenem, meropenem, ertapenem, doripenem) are fully active against *Enterobacteriaceae* and *Pseudomonas*; they are similar in gram-negative coverage to the aminoglycosides and third-generation cephalosporins. In addition, they have excellent staph and anaerobic coverage. Although effective in polymicrobial infections, they are best used in gram-negative infections.

All carbapenems are equally effective against anaerobes, as compared to metronidazole. Ertapenem will not cover *Pseudomonas*.

Anaerobes

The agent most active against anaerobes is metronidazole.

- Metronidazole has some advantages against anaerobic gram-negative bacteria in the bowel, such as *Bacteroides fragilis*.
- Clindamycin is less active against intra-abdominal anaerobes, but has some advantages against anaerobic streptococci in the mouth.
- The other agents with excellent anaerobic coverage virtually equal to metronidazole are the carbapenems and the beta-lactam/beta-lactamase combination medications (piperacillin/tazobactam, ticarcillin/clavulanate, ampicillin/sulbactam, or amoxicillin/clavulanate)
- The second-generation cephalosporins cefoxitin and cefotetan have fair activity against anaerobes but are less effective.

Skin MRSA

- TMP/SMZ, clindamycin, doxycycline, and linezolid are oral agents useful for MRSA; use them for minor MRSA infections.
- TMP/SMZ, clindamycin, and doxycycline cannot be used for MRSA bacteremia.
- Clindamycin also covers Group A strep and MSSA.

Think of MRSA cellulitis when there is purulent cellulitis or an abscess. When there is nonpurulent cellulitis, cover beta-hemolytic streptococci and MSSA, using dicloxacillin, cefazolin, cephalexin, or clindamycin.

Note

Do not treat sensitive *Staph* with TMP/SMZ or doxycycline.

CENTRAL NERVOUS SYSTEM INFECTIONS

Meningitis

> A 45-year-old man is brought to the ED with 1–2 days of fever, headache, nausea, and vomiting. On physical examination he is found to have neck stiffness and photophobia.

Meningitis is an infection or inflammation of the meninges, the connective tissue covering the CNS. Most cases arise sporadically, and the precise method of spread of the microorganism into the CNS stem is not known. Overall, most meningitis cases are caused by viruses.

- *Streptococcus pneumoniae* is the most common cause of bacterial meningitis for all patients beyond the neonatal period.
- *Neisseria meningitidis,* spread by respiratory droplets, is the most common cause of meningitis in adolescents.
- *Listeria monocytogenes* is more common in those with immune system defects, particularly of the cellular (T-cell) immune system and sometimes neutrophil defects. These defects include HIV, steroid use, leukemia, lymphoma, and various chemotherapeutic agents. Since neonates and the elderly have decreased T-cell immune function, *Listeria* is more common in them.

Note

In the past, *Haemophilus influenzae* was the most common cause of meningitis in children, but that is no longer the case with the *Haemophilus* type B vaccine.

Even with immune deficits, *Streptococcus pneumoniae* is still the *most* common etiology—it is just that *Listeria* is *more* common in these patients, as compared to fully immunocompetent patients. *Staphylococcus aureus* is more common in those who have had any form of neurosurgery because instrumentation and damage to the skin introduce the organism into the CNS. *Cryptococcus* is more common in those who are HIV positive and who have profound decreases in T-cell counts to levels <100 cells.

Rocky Mountain spotted fever (RMSF) is common in those who have been exposed to ticks in the appropriate geographic area. The areas with the highest RMSF infection are in the mid-Atlantic areas, such as the Carolinas, Kentucky, and Tennessee. Lyme disease can also cause meningitis and is more common in the Northeast, such as Massachusetts, Connecticut, New York, and New Jersey. TB and syphilis are also associated with meningitis. Viruses are the most common cause of aseptic meningitis, a syndrome in which patients present in a manner similar to bacterial meningitis, but CSF analysis mostly reveals a lymphocytic pleocytosis and bacterial cultures are negative. Viruses causing aseptic meningitis include entero viruses,

arboviruses (St. Louis encephalitis virus, West Nile virus), HIV, herpes simplex, and lymphocytic choriomeningitis virus. In the past, most of these were not diagnosed, but with the availability of PCR-based testing, more cases of aseptic meningitis are being accurately classified. Group B *Streptococcus (Streptococcus agalactiae)* is the most common cause of meningitis in the neonatal period.

The spread of the organism into the CNS can be by sporadic (unknown) mechanisms or by means of contiguous local infection or by hematogenous spread. Local infections that can lead to meningitis include otitis media, sinusitis, mastoiditis, and dental infections. Hematogenous spread could possibly occur from any infection but is more common with endocarditis and pneumonia.

Clinical Presentation. Regardless of microbiologic etiology, all forms of meningitis present with fever, photophobia, headache, nuchal rigidity (neck stiffness, positive Kernig and Brudzinski signs), as well as nausea and vomiting. Altered mental status is possible, and can make a patient appear to have encephalitis. Any form of CNS infection can present with seizures. Focal neurologic deficits can also occur, the most common being visual field and cranial nerve deficits. The most common long-term neurologic deficit from bacterial meningitis is damage to the 8th cranial nerve.

Rash is associated with several types of meningitis.

- Petechial rash is suggestive of *Neisseria*
- Rash on the wrists and ankles with centripetal spread toward the body is suggestive of RMSF
- Facial nerve palsy is suggestive of Lyme disease; the target-like erythema migrans rash of Lyme disease is seldom present by the time the meningitis develops
- Pulmonary symptoms or abnormal chest x-ray suggest TB

Diagnosis.

- LP (**essential for establishing diagnosis**)
  - Culture of the CSF (**most accurate test for bacterial meningitis**); the results are always delayed for several days, however, and are rarely available at the time the initial therapy must be instituted.
  - Protein levels are elevated most commonly with bacterial meningitis (but can be elevated in any type of meningitis).
  - Elevated protein and/or decreased glucose by themselves are relatively nonspecific findings.
  - The opening pressure can be elevated with any cause of meningitis.
- CT scan of the head
  - Best initial diagnostic test if patient has papilledema, focal motor deficits, new onset seizures, severely abnormal mental status, or immunocompromised status
  - If none of the above is present, CT scan is not needed first
  - CT scan can delay the diagnosis; if LP is delayed >20–30 min while waiting for the CT scan, give an empiric dose of antibiotics

- Gram stain has a limited sensitivity and is positive in 50–70% of patients at most; when positive, however, it has a high specificity.
- Cell count (**initially, most useful test**); although elevated cell count by itself is nonspecific, the differential of the cells is useful. Only bacterial meningitis gives thousands of cells that are all neutrophils. A mild-to-moderate elevation in lymphocytes, with several dozen to several hundred cells, can occur with viral infection, *Rickettsia*, Lyme, TB, syphilis, or fungal (cryptococcal) etiology. Normal CSF cell count is <5 cells/mm^3, which should be predominantly lymphocytes.
- **Nonbacterial meningitis** can be diagnosed according to the nature of the organism.
  - Lyme and RMSF are best detected with a specific immunologic response and serology.
  - *Cryptococcus neoformans* is detected with elevated serum and CSF cryptococcal antigen titer.
  - Syphilis is confirmed by the presence of a positive VDRL or FTA on CSF.
  - TB is rarely detected by an AFB smear; a culture for TB has a much higher yield, particularly on several repeated LPs, and PCR can also help with TB diagnosis.

Treatment.

- Vancomycin (empiric therapy of bacterial meningitis in adults because of the increasing prevalence worldwide of pneumococci with decreasing sensitivity to penicillins) plus a third-generation cephalosporin such as ceftriaxone
- For the immunocompromised or those age >50 or ≤1 month, add ampicillin to cover *Listeria* (*Listeria* is resistant to all forms of cephalosporins)
- If hospital-acquired or post-neurosurgical procedure, must cover *Pseudomonas* and MRSA: use vancomycin and cefepime, ceftazidime, or meropenem (for penicillin-allergy, replace moxifloxacin for cephalosporin) and TMP/SMX for ampicillin)
- Lyme disease: ceftriaxone
- *Cryptococcus*: amphotericin B and flucytosine initially, followed by fluconazole for HIV-positive patients (life-long or until patient is on HAART and is asymptomatic with CD4 count >100/μL for at least 3–6 months)
- Neurosyphilis: high-dose IV penicillin
- TB meningitis: same treatment as pulmonary TB but for longer duration, 9–12 months
  - For TB and bacterial (adult) meningitis, steroids are appropriate.
    - Dexamethasone decreases morbidity, mortality, and rates of deafness
    - Benefit is greatest for pneumococcal meningitis
    - Administer 15–20 min before or concurrently with antibiotics
    - Give for 4 days if bacterial meningitis is confirmed (i.e., positive Gram stain of CSF fluid or >1000 WBCs within the CSF)
    - Discontinue if etiology is nonbacterial (viral, fungal, etc.)

Clinical Pearl

In patients presenting with symptoms and signs of meningitis, treat empirically for bacterial meningitis while awaiting the LP test results.

Note

Vancomycin is used if there is a known/suspected pneumococcal resistance to penicillin or if there is a chance of staphylococcal infection after neurosurgery.

Note

The rationale for steroid use with bacterial meningitis is the inflammatory response elicited in the subarachnoid space due to bacterial cell wall lysis after antibiotics are administered; this inflammatory reaction can worsen morbidity and mortality due to bacterial meningitis.

Clinical Recall

A 65-year-old man presents to the ED with fever, stiff neck, and photophobia. Which of the following is the best empiric treatment?

A. Vancomycin, ceftriaxone, ampicillin, and dexamethasone

B. Nafcillin, ceftriaxone, and ampicillin

C. Vancomycin and ceftriaxone

D. Vancomycin, cefepime, and dexamethasone

E. Vancomycin, ceftriaxone, and ampicillin

Answer: A

Encephalitis

A young man is brought to the ED by his friends because of 1–2 days of confusion and strange behavior. He had originally complained of a headache and fever. On the day of admission he became markedly worse and is now delirious. He is generally healthy. On physical examination you find a lethargic, confused man with an elevated temperature. You are unable to determine if he has focal neurologic findings or to obtain an accurate neurologic exam because his confusion makes him unable to follow commands.

Note

Think of West Nile encephalitis when the patient has acute asymmetric flaccid paralysis.

Encephalitis is an infection of the brain, whether in the meninges or the brain parenchyma. Although any bacterial, protozoal, or rickettsial infection can cause encephalitis, most cases are caused by viruses.

- Herpes simplex (usually type I [HSV-1]) (**most common**)
- Varicella-zoster virus, CMV, enteroviruses, Eastern and Western equine encephalitis, St. Louis encephalitis, and West Nile encephalitis (less common)

Note

Encephalitis usually presents with altered mental status, erratic behavior, etc (brain parenchyma involved).

Symptoms include:

- Altered mental status with fever and headache (**clue to diagnosis**)
- Any level of neurologic deficit, from slight confusion to lethargy or coma
- Focal deficits
- Stiffness similar to that found in meningitis (making it difficult to distinguish from meningitis)
- Seizures

Diagnosis. Although CT or MRI of the head should be performed, it cannot give a specific diagnosis. HSV has a predilection for involvement of the temporal lobes, which can sometimes be seen on CT. LP is the key to the diagnosis. Formerly, a brain biopsy was necessary, but PCR (polymerase chain reaction) amplification techniques have virtually eliminated that need. PCR for HSV has a 98% sensitivity and >95% specificity, making it at least equal to the biopsy. HSV PCR may be negative early on. If imaging and clinical presentation is consistent with HSV, continue acyclovir and repeat HSV PCR in 3–5 days.

Treatment. HSV encephalitis is best treated with IV acyclovir. Although famciclovir and valacyclovir have activity against HSV, they are not available intravenously. Ganciclovir and foscarnet are active against CMV. Acyclovir-resistant herpes is treated with foscarnet.

Autoimmune Encephalitis

Autoimmune encephalitis is caused by anti-NMDA receptor antibodies. About >50% of cases are associated with ovarian teratomas.

Clinical Presentation.

- Choreoathetosis
- Psychiatric symptoms
- Seizures
- Autonomic instability
- Coma

Diagnosis. CSF anti- NMDA receptor antibodies.

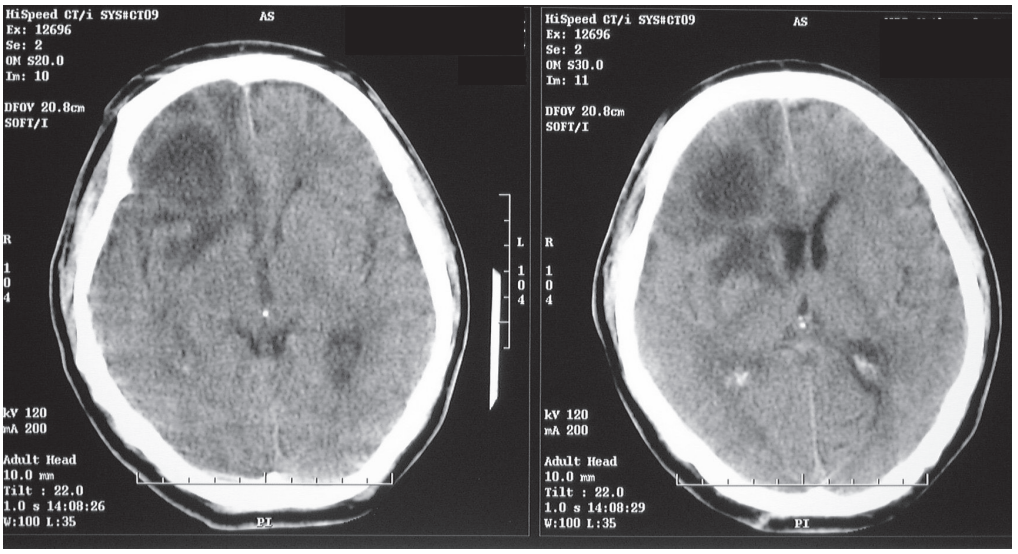
Treatment is removal of the teratoma when present; corticosteroids; rituximab; cyclophosphamide; and IVIG.

Brain Abscess

> An HIV-negative man is brought to the hospital because of a seizure. When he becomes more alert, you find that he has aphasia and weakness of the right hand and leg. CT scan of the head with contrast shows enhancement of the lesion with a "ring" around the lesion.

Brain abscess is a collection of infected material within the brain parenchyma. Bacteria can spread into the brain from contiguous infections such as otitis media, sinusitis, mastoiditis, or dental infection. Organisms may also spread through the bloodstream from endocarditis or pneumonia and seed the brain. Toxoplasmosis can reactivate in those with severe HIV disease when CD4 counts are very low (<50–100/μL). Brain abscesses most commonly have *Streptococcus* in 60–70%, *Bacteroides* in 20–40%, Enterobacteriaceae in 25–35% and *Staphylococcus* in 10%, and are often polymicrobial. Because of the diversity of the organisms potentially involved, it is difficult to have a single standard therapy.

Headache is the most common symptom. Fever can be present. Focal neurologic deficits are the initial complaint in about 60% of patients. Seizures may occur, as with any form of anatomic abnormality of the CNS. All CNS infections can cause seizures.



aic.cuhk.edu.hk/web8

Figure 7-1. CT Scan Demonstrating Large Cerebral Abscess

Diagnosis. The initial test is the CT scan. Contrast is used to help identify the lesion, although CNS malignancy enhances with contrast as well. MRI is more accurate than the CT scan, although no radiologic test alone can give the precise etiology. In the case of bacterial brain abscess, examination of the abscess fluid (obtained by stereotactic aspiration or surgical excision of the abscess) for Gram stain and culture is essential. In HIV-positive patients, 90% of brain lesions will be either toxoplasmosis or lymphoma. This is the only circumstance where empiric therapy is sufficient to establish a specific diagnosis. If the lesion responds to 10–14 days of therapy with pyrimethamine and sulfadiazine, continue to administer this therapy, as it accurately predicts cerebral toxoplasmosis.

Treatment is almost always a combination of surgical and medical management. Focus on the underlying cause.

- Surgical: stereotactic aspiration (**preferred**) or surgical excision of the abscess (rarely done because of significant complications)
- Medical: one example is penicillin, metronidazole, and a third-generation cephalosporin such as ceftazidime
  - Penicillin to cover the streptococci, metronidazole to cover the anaerobes, and ceftazidime to cover the gram-negative bacilli
  - For HIV-positive patients: pyrimethamine and sulfadiazine

HEAD AND NECK INFECTIONS

Otitis Media

Otitis media is an infection of the middle ear between the eustachian tube and the tympanic membrane. Viral upper respiratory infection can cause edema of the eustachian tube, which often leads to middle ear infection. The most common organisms are *Strep pneumoniae* (35–40%), *H. influenzae* (nontypeable; 25–30%), and *Moraxella catarrhalis* (15–20%). Viruses probably account for the rest of the cases (roughly the same breakdown of organism type and frequency that occurs in bronchitis and sinusitis).

Symptoms include ear pain, decreased hearing, and ear pain. On physical examination a red, bulging tympanic membrane is found, with loss of the light reflex. The most sensitive clinical finding is immobility of the membrane on insufflation of the ear with air. Perforation of the tympanic membrane with otorrhea occurs rarely.

Diagnosis is made through physical examination of the ear. Radiologic tests are not useful. A specific bacteriologic diagnosis can be obtained with tympanocentesis for culture, but that is rarely performed.

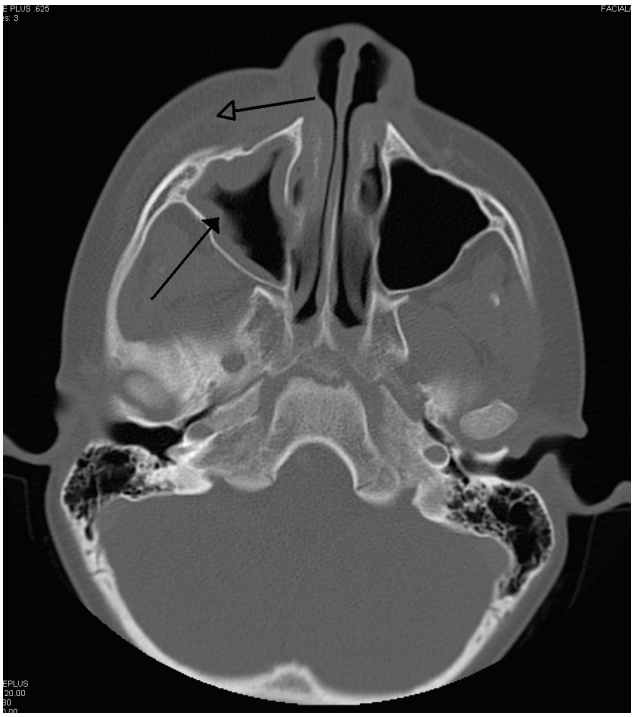
Treatment is oral amoxicillin.

- If there is no response or if the patient has been recent amoxicillin use, use amoxicillin-clavulanate; a second-generation cephalosporin (cefuroxime, loracarbef, cefprozil); or a third-generation agent (cefdinir, cefixime).
- For severe penicillin allergy, give a macrolide such as azithromycin or clarithromycin.
- New fluoroquinolones such as levofloxacin, moxifloxacin, or gatifloxacin are microbiologically acceptable but are broader coverage than needed, so do not use in children (concern for arthropathy).
- TMP/SMZ is sometimes used but is poorly active against *Streptococcus pneumoniae*.

Sinusitis

> A young woman presents with several days of facial pain, a headache, cough, fever, and discolored nasal drainage. On physical examination, tenderness over the maxillary sinuses and decreased transillumination of the maxillary sinuses are found.

Sinusitis is an infection of the sinuses. The most common site is the maxillary sinus, followed by ethmoid, frontal, and sphenoid sinuses.



Wikipedia, James Heilman, MD

Figure 7-2. Sinusitis

Viruses are responsible for most cases of sinusitis. Bacterial organisms that cause sinusitis are the same ones causing otitis media. Bacterial infection is more likely in one of the following situations:

- Persistent symptoms >10 days
- Severe symptoms of fever lasting 3–4 days
- Double-sickness (worsening symptoms following a period of improvement over 3–4 days)

Symptoms include:

- Facial pain
- Postnasal drainage, purulent nasal drainage
- Headache (**common**) is worse when leaning forward
- Fever (50% of cases)
- Tooth pain (due to proximity of sinuses to the teeth)

Diagnosis. Obvious cases of sinusitis do not always need radiologic confirmation prior to treatment. Sinus x-rays are of little value, and routine imaging as a rule is not recommended. If imaging is required because of concern for complications, uncertain diagnosis, or lack of response to treatment, CT scan of the sinuses is the test of choice since it provides greater detail. For those who are immunocompromised, CT should be done to evaluate for fungal infection.

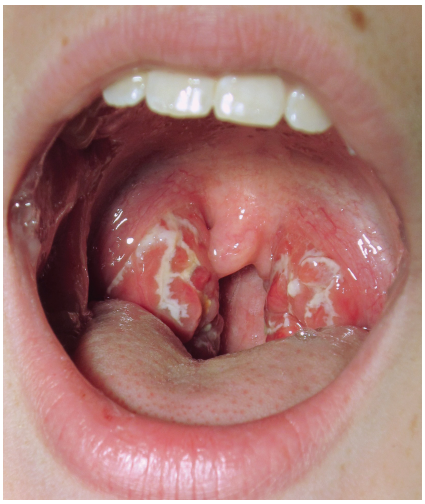
Treatment.

- For uncomplicated sinusitis (mild or acute), use NSAIDs and decongestants, e.g., oral pseudoephedrine or oxymetazoline spray; most cases resolve in 7–10 days
- If antibiotics are needed, amoxicillin-clavulanate is first-line; use doxycycline for penicillin allergy

Pharyngitis

Pharyngitis is irritation or inflammation of the back of the throat (or the pharynx). Although most cases are caused by viruses, the most important cause is group A beta-hemolytic streptococci (*S. pyogenes*) (only 5–15% of cases) because that could progress to rheumatic fever or glomerulonephritis.

Sore throat with cervical adenopathy and inflammation of the pharynx with an exudative covering is highly suggestive of *S. pyogenes*. Most viruses do not give an exudate, although the Epstein-Barr virus can. Mild *S. pyogenes* infections may not give an exudate, which is one of the reasons diagnostic testing is useful. Hoarseness and cough are not suggestive of pharyngitis.



Wikipedia, James Heilman, MD

Figure 7-3. Strep Throat

Diagnosis. The Centor criteria include 4 findings:

- Fever by history
- Tonsillar exudates
- Anterior cervical lymphadenopathy
- Absence of cough

Centor criteria <3 should not be treated or tested, while criteria 3 or 4 should get a rapid antigen detection test. If that is negative and the patient is high risk for complications, a throat culture should be done.

The rapid streptococcal antigen test is 80% sensitive but >95% specific. A positive test can be considered the equivalent of a positive culture, whereas a negative test should be confirmed with a culture.

Treatment is penicillin or amoxicillin. Use macrolides, clindamycin, or oral, first-generation cephalosporins for penicillin-allergy.

A rare complication of pharyngitis is **Lemierre syndrome**. Think of this in young adults with prolonged/severe pharyngitis, recent sore throat, persistent fever while on appropriate antibiotics, and neck pain/swelling.

- Etiology is septic thrombophlebitis of the internal jugular vein resulting in metastatic pulmonary infections due to septic emboli
- Causative organism is *Fusobacterium necrophorum*
- Diagnosis is made with CT contrast of the neck.
- Treatment is anything that covers anaerobes, i.e., ampicillin/sulbactam, clindamycin, carbapenem.

Influenza

Influenza is a systemic viral illness from influenza A or B, usually occurring in an epidemic pattern and transmitted by droplet nuclei. Influenza can lead to damage to the respiratory epithelium, leading to sinusitis, otitis media, bronchitis, and pneumonia.

Patients present with a systemic illness characterized by fever, myalgias, headache, and fatigue. Upper respiratory symptoms tend to predominate. These include runny nose (coryza), nonproductive cough, sore throat, and conjunctival injection.

Diagnosis is initially confirmed with rapid antigen detection methods of swabs or washings of nasopharyngeal secretions. Viral culture is the most accurate test but is usually not available rapidly enough to make it useful in acute patient management.

Treatment.

- For symptomatic disease
  - Acetaminophen and antitussives
  - Oseltamivir and zanamivir, neuraminidase-inhibitors specific for influenza A and B (use within 48 hours of onset of symptoms)
- Amantadine and rimantadine should not be used in the empiric therapy of influenza.
- **Influenza vaccination** is recommended annually for the general public.
  - Most important candidates include those who have chronic lung/cardiac disease or are immunosuppressed, pregnant women (any trimester), residents of chronic care facilities, health-care workers, and those with diabetes/renal dysfunction
  - Influenza vaccine contains egg protein, but because studies show that severe reaction in those with true egg protein allergy is rare, no precaution is needed.
  - As with any vaccine administration, monitor patients for any allergic manifestations.

Note

For influenza, chemoprophylaxis with oseltamivir should be initiated as soon as possible (and no later than 48 hours after exposure) and then continued for 7 days.

Note

- Flu vaccine is indicated annually for everyone age >6 months.
- Flu vaccine contains egg protein, but because severe reaction in those with egg protein allergy is rare, no precaution is needed. Monitor patients afterward.

Clinical Recall

An elderly, HIV-positive man comes to the ED with fever, headache, and muscle weakness. Imaging shows a brain abscess. Which of the following is the most appropriate next step in management?

A. Brain biopsy to confirm pathogen

B. Ceftriaxone, vancomycin, ampicillin, and steroids

C. 10–14 days of therapy with pyrimethamine and sulfadiazine

D. HSV PCR followed by IV acyclovir

E. LP with culture of CSF fluid

Answer: C

LUNG INFECTIONS

Bronchitis

A 63-year-old man presents with a cough productive of yellowish sputum for several days. He has smoked 1 pack of cigarettes a day for 30 years. On physical examination the lungs are clear. His temperature is 38.3 C (101 F). Chest x-ray is normal.

Bronchitis is an infection of the lung, limited to the bronchial tree with limited involvement of the lung parenchyma. Acute exacerbations of chronic bronchitis (COPD) are often difficult to distinguish from a pneumonia until chest x-ray is performed.

- **Acute bronchitis** is an acute inflammation of the tracheobronchial tube. The vast majority of cases are caused by viruses. *S. pneumoniae* and *H. influenzae* have not been implicated. A small percentage of nonviral cases are due to *M. pneumoniae*, *C. pneumoniae*, and *B. pertussis*.
- **Chronic bronchitis** is caused by agents similar to those causing sinusitis and otitis media: *Streptococcus pneumoniae*, nontypeable *H. influenzae*, and *Moraxella*. Viruses account for a significant percentage but are often not confirmed. Cigarette smoking is the most common cause.

Clinical Presentation.

- Cough often with sputum production (discolored sputum suggests a bacterial etiology, but it is impossible to determine the specifics by that characteristic alone)
- Clear lungs (common) (however, lung exam may reveal rales)
- Signs of consolidation, e.g., increased fremitus, are absent
- Possible low-grade fever, but patients are more often afebrile

Diagnosis. Signs of respiratory infection, such as cough and sputum, with a normal chest x-ray confirm the diagnosis.

Note

Cigarette smoking is the most common cause of chronic bronchitis. Even 1 cigarette per day is enough to paralyze the cilia, which clear the bronchial tree of mucus and inhaled impurities for 24 hours.

Treatment.

- Mild acute cases: no treatment needed
- Acute exacerbations of chronic bronchitis: amoxicillin, doxycycline, or TMP/SMZ (if there has not been recent antibiotic use)
- Repeat infections or if no response to amoxicillin, one of the following:
  - Amoxicillin/clavulanate
  - Clarithromycin
  - Azithromycin
  - Oral second- or third-generation cephalosporin
  - New fluoroquinolone: gemifloxacin, levofloxacin, or moxifloxacin

Lung Abscess

A 58-year-old alcoholic man was admitted last night for several weeks of cough, sputum, and fever. He has lost 15 pounds and is feeling weak. On initial examination he is febrile and appears thin. He has very poor dentition. The lung examination is normal. The patient also exhibits a foul odor on the oral examination.

Lung abscess is necrosis of the pulmonary parenchyma caused by microbial infection.

- 90% have at least some anaerobes involved
- The most commonly implicated anaerobes are *Peptostreptococcus*, *Prevotella*, and *Fusobacterium* species, which are oral anaerobes found in the gingival crevices
- 45% only anaerobic, 45% mixed with aerobes, 10% aerobes only
- Aerobic bacteria, most frequently involved are *S. aureus, E. coli, Klebsiella,* and *Pseudomonas*

85–90% of cases have a clear association with periodontal disease or some predisposition to aspiration (e.g., altered sensorium, seizures, dysphagia). Pulmonary infarction, cancer, and vasculitis (like Wegener granulomatosis) are examples of noninfectious causes of lung cavities.

Patients present with the usual symptoms of pulmonary infection, such as fever, cough, sputum production, and chest pain, plus the following:

- Putrid, foul-smelling sputum (60–70% of cases)
- A more chronic course, i.e., several weeks of weight loss, anemia, and fatigue prior to diagnosis (likely due to the 1–2 week delay between the aspiration of oral contents and the development of necrosis and cavitation)

Diagnosis. Sputum for Gram stain and culture will not be able to show the causative anaerobic organism in a lung abscess. Chest x-ray in an abscess will often show a thick-walled cavitary lesion. Chest CT can help define the exact extent of the cavity. In the upright position the lower lobes are the most common sites of aspiration. In the supine position the posterior segment of the right upper lobe is the most common site. Aspiration of the abscess fluid is necessary for a specific bacteriologic diagnosis.

Treatment. In the absence of specific microbiologic diagnosis, clindamycin is good empiric coverage for the "above the diaphragm" anaerobes most often found. Penicillin is also acceptable.

In contrast to most abscesses where drainage is the rule, lung abscesses rarely require drainage in the antibiotic era. Most respond to antimicrobial therapy and drain spontaneously by communicating with larger bronchi. Therefore, the answer to the question, *what is the best initial therapy for a lung abscess*, is antibiotics such as clindamycin, not drainage.

Pneumonia

Pneumonia, a leading cause of death in the United States, is an infection of the lung parenchyma. Causes include:

- Community-acquired pneumonia (CAP)
  - *S. pneumoniae* (**most common cause** when an actual cause is identified)
  - In children age <5, viruses (**most common cause**)
  - Subsequent causes may vary, but S. *pneumoniae* is always number 1
- Hospital-acquired pneumonia (HAP) or ventilator-associated pneumonia (VAP)
  - Gram-negative bacilli such as *E. coli*, the other *Enterobacteriaceae*, or Pseudomonas
  - MRSA

Table 7-1. Frequency of Infectious Agents Causing Pneumonia

"Typical"	40–60%
Strep pneumoniae	15–35%
Haemophilus	2–10%
Moraxella	<5%
"Atypical"	10–30%
Legionella	0–15%
Mycoplasma	10%
Chlamydia	5–10%
Viral	2–20%
Unknown	30–60%

Specific predispositions are as follows:

- *Haemophilus influenzae*: smokers, COPD
- *Mycoplasma*: young, otherwise healthy patients
- *Legionella*: epidemic infection in older smokers, particularly when located near infected water sources, such as air-conditioning systems

Note

Pneumonia is the only cause of death from an infectious disease in the top 10 causes of death in the United States.

Note

With pneumonia diagnosis, a particular predisposing condition is not essential (although some conditions do predispose to having pneumonia, i.e., cigarette smoking, diabetes, alcoholism, malnutrition, obstruction of the bronchi from tumors, and immunosuppression in general).

Neutropenia and steroid use predispose to *Aspergillus* infection.

- *Pneumocystis jiroveci* (formerly *carinii*) pneumonia: HIV-positive persons with <200 CD4 cells not on prophylaxis
- *Coxiella burnetii* (Q-fever): exposure to animals, particularly when they are giving birth
- *Klebsiella*: alcoholics
- *Staphylococcus aureus* (MRSA): following viral syndromes or viral bronchitis, especially influenza; cavity infiltrates
- *Pseudomonas aeruginosa*, *Burkholderia cepacia*, *Stenotrophomonas*: structural lung disease (bronchiectasis including CF; recent steroid use; broad-spectrum antibiotics in past month)
- *Coccidioidomycosis*: exposure to the deserts of the American Southwest, particularly Arizona; associated with erythema nodosum and monoarthritis
- *Chlamydia psittaci*: birds
- *Blastomycosis*: skin lesions; bone and prostate involvement
- *Histoplasma capsulatum*: exposure to bat or bird droppings, spelunking (recreational cave exploration); oral ulcers; hepatosplenomegaly; pancytopenia; hilar lymphadenopathy; cavitary lung lesions
- *Bordetella pertussis*: cough with whoop and post-tussive vomiting
- *Francisella tularensis*: hunters, or exposure to rabbits; abrupt fever; hilar lymphadenopathy; pleural effusions
- *SARS, Avian influenza*: travel to Southeast Asia
- *Bacillus anthracis*, *Yersinia pestis*, and *Francisella tularensis*: bioterrorism
- *Invasive aspergillosis*: neutropenic fever; "halo sign" on CT scan; possible positive serum galactomannan (treatment is voriconazole)

Patients with pneumonia present with cough, fever, and often sputum production. Severe pneumonia of any cause may present with dyspnea. The quality and degree of sputum produced might provide useful clues to the microbiologic etiology of pneumonia at the initial presentation. Bacterial infections such as *S. pneumoniae*, *Haemophilus*, and *Klebsiella* have significant purulent sputum production because they are infections of the alveolar air space.

- The sputum with *S. pneumoniae* is described as rusty. The "rust" is simply hemoptysis. As the blood oxidizes, it becomes brownish-red color. Any form of persistent cough may be associated with hemoptysis, however, and hemoptysis by itself is nonspecific.
- The sputum with *Klebsiella pneumoniae* is described as currant jelly. This is simply hemoptysis with mucoid characteristics from a combination of the necrotizing nature of *Klebsiella* with the organism's thick mucopolysaccharide coating.
- Interstitial infections such as those caused by *Pneumocystis* pneumonia (PCP), viruses, *Mycoplasma*, and sometimes *Legionella* often give a nonproductive or "dry" cough.

Any cause of pneumonia may be associated with pleuritic chest pain. This is pain worsened by inspiration. Commonly, pleuritic pain is associated with lobar pneumonia, such as that caused by *Pneumococcus*. This is because of localized inflammation of the pleura by the infection. Lobar pneumonia is the type most commonly associated with signs of consolidation on examination.

On physical examination pneumonia presents with rales, rhonchi, or signs of lung consolidation, including dullness to percussion, bronchial breath sounds, increased vocal fremitus, and egophony (E to A changes).

The respiratory rate is essential in determining the severity of a pneumonia. The respiratory rate is often a close correlate of the level of oxygenation. Severe pneumonia leads to hypoxia, which leads to hyperventilation.

Organism-specific presentations are as follows:

- *Mycoplasma*: dry cough and chest soreness. Dyspnea is rare. Bullous myringitis and anemia from hemolysis from cold agglutinin disease are occasionally present. Patients with *Mycoplasma pneumoniae* rarely need to be admitted to the hospital; therefore, any patient presented to you as an inpatient is less likely to have *Mycoplasma*.
- *Legionella*: CNS manifestations such as confusion, headache, and lethargy. GI manifestations include diarrhea and abdominal pain.
- PCP: marked dyspnea, particularly on exertion, with chest soreness with cough in an HIV-positive person. Patients invariably have AIDS with CD4 count <200/μL.

Diagnosis. The most important initial test for pneumonia is the chest x-ray, which both shows the presence of disease and gives the initial clues to determining the diagnosis.

- Infiltrates are either localized to a single lobe of the lung or bilateral and interstitial (**most important clue**).
- *S. pneumoniae* (and other causes of "typical" pneumonia) usually appear as a lobar pneumonia with parapneumonic pleural effusion.
- Interstitial infiltrates are associated with PCP, viral, *Mycoplasma*, *Chlamydia*, *Coxiella*, and sometimes *Legionella* pneumoniae.
- Sputum culture should be obtained for both Gram stain as well as culture. Sputum culture is the **most specific diagnostic test** for lobar pneumonia, such as with *S. pneumoniae*, *Staphylococcus*, *Klebsiella*, and *Haemophilus*.
- The other "atypical" organisms (viral, *Mycoplasma, Chlamydia, Coxiella,* etc.) will not show up on Gram stain or regular bacterial culture for various reasons.
- Bronchoscopy, thoracentesis, pleural biopsy, or culture of pleural fluid (infrequently needed)
- Open lung biopsy (**most specific diagnostic test**)

Organism-specific diagnostic methods are as follows:

- *Mycoplasma*: specific serologic antibody titers; cold agglutinins have both limited specificity and sensitivity
- *Legionella*: specialized culture media with charcoal yeast extract, urine antigen tests, direct fluorescent antibodies, and antibody titers
- PCP: bronchoalveolar lavage, increased LDH
- *Chlamydia pneumoniae*, *Coxiella*, *Coccidioidomycoses*, and *Chlamydia psittaci*: specific antibody titers

Note

The urine *Legionella* test is not sensitive.

Note

CURB-65 indicates need for hospitalization in pneumonia:

Confusion

Uremia

Respiratory distress

Blood pressure low

Age >65

Treatment. Mild disease can be treated outpatient, and more severe disease requires inpatient IV antibiotics. Severity is determined by the following:

- Degree of hypoxia, such as a pO2 <60 mm Hg, oxygen saturation <94% on room air, or respiratory rate >30/min
- Confusion/disorientation
- Uremia
- Hypotension (systolic BP <90 mm Hg and diastolic BP <60 mm Hg)
- High fever
- Hypothermia
- Hyponatremia
- Leukopenia (WBC <4,000/mm^3)
- Rapid pulse (>125/min)
- Dehydration as determined by elevated BUN

Note

Co-morbidities include chronic heart failure, COPD, asthma, DM, kidney disease, nephrotic syndrome, malignancy, alcoholism, smoking asplenism, and immunosuppression.

Patients with serious underlying disease often do better inpatient with IV medication.

The specific organism causing pneumonia is rarely known when the initial treatment decision must be made.

CAP.

- Inpatient treatment
  - Levofloxacin, moxifloxacin, or gatifloxacin
  - Second- or third-generation cephalosporin such as cefotaxime or ceftriaxone plus a macrolide antibiotic, e.g., azithromycin, clarithromycin, doxycycline
- Outpatient treatment
  - Macrolides, e.g., azithromycin or clarithromycin only for those who are young and healthy, with low risk of resistance; use a respiratory fluoroquinolone for those with co-morbities or recent antibiotics
  - Oral second- and third-generation cephalosporins or amoxicillin/clavulanate + a macrolide or doxycycline to cover the atypical pathogens

Table 7-2. Empiric Therapy of Community-Acquired Pneumonia

Outpatient	Inpatient
Young, healthy patients with no co-morbidities or antibiotic use in preceding 3 months Azithromycin, clarithromycin, or doxycycline **Respiratory fluoroquinolones, comorbidities, or antibiotic use in preceding 3 months** Levofloxacin, moxifloxacin, gemifloxacin, or oral beta-lactam + a macrolide or doxycycline	Respiratory fluoroquinolones (levofloxacin, moxifloxacin, or gemifloxacin) or Second- or third-generation cephalosporins (cefuroxime or ceftriaxone) combined with a macrolide or doxycycline or Beta-lactam/beta-lactamase combination drug (ampicillin/sulbactam; ticarcillin/clavulanate; piperacillin/tazobactam) combined with doxycycline or a macrolide • If risk factors for CA-MRSA, use above therapy + vancomycin or linezolid or ceftaroline + a macrolide or doxycycline • If risk factors for *Pseudomonas*, use antipseudomonal beta-lactam (like cefepime or meropenem) + ciprofloxacin; for penicillin-allergy, use a respiratory quinolone + aztreonam

HAP.

Those patients who develop pneumonia after 5–7 days in the hospital are at increased risk of infection from drug-resistant, gram-negative bacilli (*Pseudomonas*, *Klebsiella*, *E. coli*, etc.) or gram-positive bacilli such as MRSA.

- Third-generation cephalosporin with antipseudomonal activity (e.g., ceftazidime) or carbapenem (e.g., imipenem)
- Beta-lactam/beta-lactamase inhibitor combinations (such as piperacillin/tazobactam) and vancomycin or linezolid to cover MRSA.
- Possible addition of an aminoglycoside (gentamicin, tobramycin, amikacin) to empiric gram-negative coverage

Treatment of specific organisms is as follows:

- *Haemophilus influenzae*: second- or third-generation cephalosporins
- *Mycoplasma*: macrolides, doxycycline, or a quinolone
- *Legionella*: macrolides, doxycycline, or a quinolone
- *Pneumocystis* pneumonia: TMP/SMZ
  - Use steroids if the infection is severe (severe is defined as arterial pO2 <70 mm Hg or A-a gradient >35 mm Hg).
  - If patient is allergic to TMP/SMZ, use IV pentamidine or atovaquone. (Dapsone or atovaquone can be used prophylactically).
- *Coxiella burnetii* (Q-fever): doxycycline or erythromycin

Note

With HAP, adding an aminoglycoside to empiric gram-negative coverage is done for synergy and to ensure that patient gets at least one drug if the bacteria are multi-drug resistant. Antibiotic therapy can then be adjusted when culture results (sputum, blood, bronchoalveolar lavage, and/or pleural) become available.

- *Klebsiella*: third-generation cephalosporin and the other drugs for gram-negative bacilli
- *Staphylococcus aureus*: semisynthetic penicillin (oxacillin, nafcillin, etc.) if methicillin-sensitive; in the nosocomial setting, isolates are invariably methicillin-resistant, and vancomycin or linezolid is administered
- *Coccidioidomycosis*: no treatment for primary pulmonary disease; treatment used only for disseminated disease or in those with pulmonary disease who are immunosuppressed.
  - Mild disease: fluconazole or itraconazole
  - Life-threatening disease: amphotericin

Pneumococcal vaccine

For those who are immunocompromised, the PPSV23 should be given 8 weeks after the PCV13 vaccine.

Table 7-3. Pneumococcal Immunization

Risk Group	PCV13	PPSV23
Those who are immunocompromised and age ≥65	Recommended	Recommended 1 year after PCV13; revaccinate after 5 yrs if age <65 at first dose
Those who are immunocompromised and have chronic heart/lung/liver disease, DM, alcoholism, or smoke	Not recommended	Recommended; revaccinate after 5 yrs if age <65 at first dose
Those with functional or anatomic asplenia	Recommended	Recommended
Those who are immunocompromised and have HIV, lymphoma, Hodgkin, nephrotic syndrome	Recommended	Recommended

Note

In generally healthy persons vaccinated age >65, a single dose of pneumococcal vaccine is enough to confer lifelong immunity.

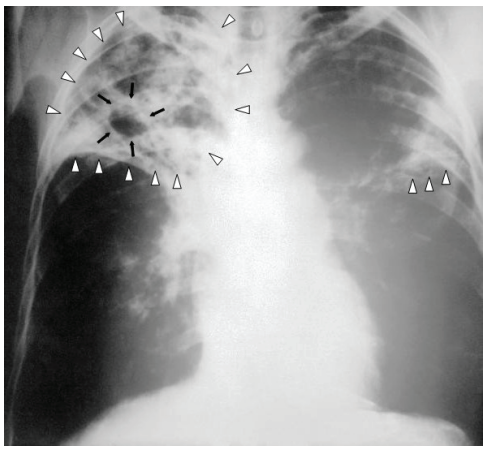
Tuberculosis

A 37-year-old resident of a maximum-security correctional facility has been having a cough, voluminous sputum production and fever for the last few weeks. He has had a 10-pound weight loss and feels very weak.

TB is an infection with *Mycobacterium tuberculosis*. Worldwide, TB is one of the top 3 causes of all deaths.

TB is spread exclusively by person-to-person transmission by means of respiratory droplet infection. There is no animal reservoir of the disease. Bacillus Calmette-Guérin (BCG) vaccination is used in many parts of the world outside the United States to try to prevent infection. It is, at best, 50% effective and is never indicated for routine use in the United States.

Besides immigrants, TB occurs predominantly in persons with specific risk for exposure, such as alcoholics, healthcare workers, prisoners, homeless shelter residents, nursing home residents, and chronically debilitated patients whose weakened immune systems allow for more frequent re-activation of latent infection. Impairment of T-cell–mediated cellular immunity is the most significant defect associated with re-activation. This is why steroid use, organ transplantation, leukemia, lymphoma, and HIV are such important risk factors.



Centers for Disease Control and Prevention

Figure 7-4. Tuberculosis X-ray

Patients present with cough, sputum, fever, and an abnormal lung exam. They may be impossible to distinguish clinically from those with pneumonia.

Even when untreated, TB usually takes up to 5 years to become fatal.

- Weight loss (common) because of the chronicity of the infection
- Night sweats
- Cough >3 weeks
- Hemoptysis
- Presentation depends on site involved
  - Any part of the body can be involved
  - In extrapulmonary TB, the **lymph node** (adenitis), meningeal, GI, and GU are most commonly seen
  - Can occur outside lungs (15–20% of cases)

Diagnosis. Latent TB is diagnosed with a positive PPD or IGRA in the absence of symptoms, plus a normal chest x-ray.

- Chest x-ray is the **best initial test**, as it is with all forms of pulmonary infection.
  - Apical involvement with infiltrates and sometimes cavitation is the most common finding.
  - Adenopathy, effusion, and calcified nodules (Ghon complex) are associated findings.

Note

Nearly 25% of the world's population has been exposed to TB and would be reactive to PPD testing. Until the middle of this century, TB was the most common cause of death in the United States, but it is now at an all-time low, with <15,000 cases per year (over half of those are recent immigrants).

Note

Lymph node involvement (adenitis) is the most frequently involved **extrapulmonary site** in TB.

Note

If sputum AFB stain is positive, that is usually the trigger to start treatment for TB.

- Sputum examination with specific staining for AFB allows specific diagnosis (false-negative in 25% of cases).
  - Sputum or tissue culture is the **gold standard**, but takes up to 6 weeks to grow and is not often available to guide initial therapy. The culture is also necessary in order to do sensitivity testing.
  - If sputum AFB stain is positive, that is usually the trigger to start treatment for TB.
  - If sputum AFB stain is unrevealing, consider other diagnostic tests: thoracentesis (to examine pleural fluid), gastric aspirate in children, biopsy or FNA of specific extrapulmonary organ involved, and lumbar puncture with meningitis.
- Pleural biopsy is the single most sensitive diagnostic test. A single pleural biopsy can have up to 75% sensitivity. TB will give caseating necrosis on biopsy of any tissue. Pleural fluid of adenosine deaminase is helpful in diagnosing pleural TB.

Do not use PPD testing to diagnose acute cases of TB. PPD is relatively insensitive and nonspecific particularly with acute illness. Use IGRA for screening in patients with a history of BCG, high risk of progression, or those who will not likely return to be tested.

Clinical Pearl

Newer tests may provide TB sensitivity testing in a few weeks, thus the period of using 4 drugs is significantly shortened.

Treatment. Initial therapy of TB before the results of sensitivity testing are known consists of 4-drug therapy with isoniazid (INH), rifampin (Rif), pyrazinamide (PZA), and ethambutol (ETB).

- All 4 drugs are continued for the first 2 months or until sensitivity testing is known.
- PZA and ETB are then discontinued, and treatment continues with INH and rifampin for another 4 months. That means routine therapy last for 6 months.
- The fourth drug, ETB, is given if the sensitivity is not known.
- The only forms of TB that must be treated for more 6 months are TB meningitis (12 months), TB in pregnancy (9 months), and osteomyelitis.
- Those who are HIV-positive may be treated for 6–9 months, but there is no clear evidence that 9 months is necessary, i.e., even in HIV-positive persons, 6 months of therapy is effective.
- INH use should generally be combined with vitamin B6 (pyridoxine) to prevent peripheral neuropathy that can be a side effect of INH.

Pregnant patients should not receive PZA or streptomycin. Steroid use with TB medications is only your answer for TB meningitis and TB pericarditis.

All the TB medications can cause liver toxicity, except streptomycin. Other side effects include:

- INH causes peripheral neuropathy due to pyridoxine deficiency.
- Rifampin is associated with causing a benign change in the color of all bodily fluids to orange/red.
- Ethambutol is associated with optic neuritis, which can cause color blindness and other visual disturbances.
- PZA can cause a benign hyperuricemia (do not treat the hyperuricemia unless there are symptoms/history of gout)

Diagnosis and Treatment of Latent TB Infection. The PPD test and IGRA are used to screen asymptomatic populations at risk of TB to see if they have been exposed and are at increased risk of re-activating the disease. The AFB stain and culture of the affected tissues should be performed. PPD is considered positive based on the amount of induration of the skin 48–72 h after the intradermal (not subcutaneous) injection of the PPD. Erythema is irrelevant. A positive PPD or IGRA roughly indicates a 10% lifetime risk of developing TB in HIV-negative persons. Most of the active cases will develop within the first 2 years after converting to a positive test. HIV-positive persons have a roughly 7–10% risk per year of developing active disease. Previous BCG vaccination does not alter these recommendations. The cutoffs are as follows:

≥5 mm:

- Close contacts of active TB cases
- HIV-positive persons
- Abnormal chest x-ray consistent with old, healed TB
- Steroid use or organ transplantation recipients

≥10 mm: High-risk groups, such as healthcare workers, prisoners, and nursing home residents; recent immigrants (within 5 years) from areas with a high prevalence; homeless patients; persons with immunocompromise other than those described, such as those with leukemia, lymphoma, diabetics, dialysis patients, and injection drug users who are HIV-negative or whose HIV status is unknown; and children <4 years of age, or infants, children, and adolescents exposed to adults at high risk of TB.

≥15 mm: Low-risk populations, i.e., *not* the people described, i.e., people who should never have been tested in the first place

Two-Stage Testing: All patients who have not had a recent PPD test but now show some reactivity that is <10 mm should have a second test within 2 weeks, to make sure the first test was not a false-negative. A reaction of >10 mm on the second test is simply a positive test, not a recent converter. You cannot make a PPD-negative person become positive with repeated testings.

- Anyone who tests positive on the PPD test or IGRA should have a chest x-ray to see if they have early asymptomatic evidence of TB on their film.
  - Those with abnormal chest x-ray should have 3 sputum AFB stains done to see if they have active disease.
  - Positive AFB stains indicate the need to start the 4 TB drugs described.
- Anyone with a positive PPD or IGRA but no evidence of active disease should receive 9 months of INH or 4 months of rifampin.
- Although 6 months of INH/B6 is an acceptable alternative, the recommendation is that all patients, including those who are HIV positive, should receive the same 9-month course of therapy. (Previously, this was referred to as "prophylaxis"; today, this is called "treatment of latent TB.")

The IGRA is not altered at all with previous BCG vaccine. The IGRA has the same meaning and treatment as a positive PPD skin test. Patients who received the BCG or are unlikely to return to have the PPD read should have IGRA instead of PPD. Previous BCG will not make the IGRA positive.

Note

For TB, **active disease can be excluded** with one of the following conditions:

- Normal chest x-ray
- Abnormal chest x-ray + 3 negative AFB sputum stains

Clinical Recall

Which of the following is not an indication for hospitalization in patients with pneumonia?

A. pO2 50 mm Hg

B. Creatinine 2.5 mg/dL

C. Temperature 104 F

D. Leukocytosis 11,000

E. Underlying COPD

Answer: D

GASTROINTESTINAL INFECTIONS

Infectious Diarrhea/Food Poisoning

A 27-year-old medical student leaves class at 12:30 to go to lunch. At 3:00 she starts to have repeated episodes of diarrhea. The diarrhea contains blood and mucus. She is also febrile and has abdominal pain.

Most infectious diarrhea is caused by contaminated food and water, so the overlap between infectious diarrhea and food poisoning is considerable.

There are several types of food poisoning, such as *Bacillus cereus* and *Staphylococcus aureus*, which present predominantly with vomiting, so the two terms are not entirely synonymous.

A wide variety of agents can cause food poisoning.

- *Campylobacter* (most common)
- *Salmonella* (most commonly associated agent with contaminated poultry and eggs)
- *E. coli* (most common cause of travelers' diarrhea; produces a wide spectrum of disease depending on whether it makes toxin or is invasive)
  - *E. coli* 0157:H7 is associated with undercooked hamburger meat.
  - *Bacillus cereus* is associated with fried rice; the rice becomes contaminated with bacillus spores, and as it is prepared for serving it is warmed only at a moderate temperature not hot enough to kill the spore.
  - *Giardia lamblia* and cryptosporidiosis are acquired from contaminated water sources that have not been appropriately filtered, such as fresh water on a camping trip. Cryptosporidiosis is also associated with HIV, particularly when there is profound immunosuppression and CD4 <50 cells.

- There are several types of *Vibrio* causing human disease.
  - *V. cholera* (very rare in the United States)
  - *V. parahaemolyticus* (associated with ingestion of contaminated shellfish)
  - *V. vulnificus* (associated with ingestion of raw shellfish); causes severe disease in those with underlying liver disease; also associated with iron overload and bullous skin lesions
- Viral infections such as rotavirus or Norwalk agents (very common in children)
- Ciguatera fish toxin, most commonly in red snapper and grouper
- Clostridia associations are as follows:
  - *C. difficile* with previous antibiotic use
  - *C. botulinum* with ingestion of infected canned foods
  - *C. perfringens* with ingestion of meat contaminated with spores due to unrefrigeration

Although it is important to be familiar with these associations, virtually any food can be contaminated by almost any organism. The most important thing is not what food you eat but whose dirty hands touched your food and what were they contaminated with.

Clinical Presentation.

- Presence or absence of blood in the stool (**most important feature**); blood is most commonly associated with invasive enteric pathogens such as *Salmonella*, *Shigella*, *Yersinia*, invasive *E. coli*, and *Campylobacter*
- The time between ingestion of food and the diarrhea is less important than the presence of blood.
- The invasive enteric pathogen may be causing infection in the absence of blood, and the absence of blood does not exclude them.
- *Campylobacter* is rarely associated with Guillain-Barré syndrome.
- Scombroid poisoning causes symptoms within a few minutes after eating scombroid fish (tuna, mackerel, mahi mahi), which may contain a lot of histamine: rash, diarrhea/vomiting, and wheezing, along with a burning sensation in the mouth, dizziness, and paresthesias.
- Ciguatera fish toxin causes symptoms within 2–6 hours (there is no specific treatment)
  - Paresthesias, numbness, nausea/vomiting/abdominal cramps
  - Neurologic symptoms (weakness, reversal of hot-cold sensations) in severe disease can be progressive and debilitating
  - Cardiovascular symptoms (hypotension) in severe disease
- *E. coli* 0157:H7 and *Shigella* are associated with hemolytic uremic syndrome (HUS).
- *Bacillus cereus* and *Staphylococcus* predominantly present with vomiting within 1–6 hours of their ingestion because they contain a preformed toxin. They can cause diarrhea later.
- *Giardia*, *Cryptosporidium*, *Cyclospora*, and most other protozoans do not cause bloody diarrhea. The major protozoan associated with blood in the stool is *Entamoeba histolytica*.
- Viruses can give voluminous watery diarrhea but do not cause bloody diarrhea.

Note

Incubation times are helpful only if there is a group outbreak and you can pinpoint a common source of contamination. In other words, the last thing you eat is not necessarily the thing that was contaminated.

Diagnosis. Stool studies should not be sent unless there is diarrhea for more than 1 week. *Giardia* and *Cryptosporidia* are detected by direct examination of the stool for the parasites, as well as for their eggs. A special modified AFB stain is necessary to detect *Cryptosporidia*. Stool ELISA is also used for *Giardia*.

Treatment. Therapy is determined by the severity of disease. Mild infections with the invasive pathogens and viruses usually require only oral fluid and electrolyte replacement. More severe infections, such as those producing high fever, abdominal pain, tachycardia, and hypotension, require IV fluids and oral antibiotics.

The specific etiology is rarely known when the initial treatment decisions must be made. The best initial empiric therapy for an invasive pathogen is a fluoroquinolone, e.g., ciprofloxacin.

Organism-specific therapy is as follows:

- *Campylobacter*: erythromycin
- *Giardia*: metronidazole
- *Cryptosporidium*: control of underlying HIV disease with antiretrovirals, nitazoxanide
- Nitazoxanide is the first truly useful therapy for cryptosporidiosis.
- Scombroid: antihistamines such as diphenhydramine

HEPATIC INFECTIONS

Viral Hepatitis

An 18-year-old woman presents at the ED with several days of nausea, vomiting, and fever. She uses no medications. She reports unprotected sex. Her stool is light in color. On physical examination she is jaundiced.

Viral hepatitis is an infection of the liver caused by hepatitis A, B, C, D, or E.

- **Hepatitis A and E** are transmitted by contaminated food and water. They are orally ingested and have an asymptomatic incubation period of several weeks, with an average of 2–6 weeks. They cause symptomatic disease for several days to weeks, have no chronic form, and do not lead to either cirrhosis or hepatocellular carcinoma.
- **Hepatitis B, C, and D** are transmitted by the parenteral route. They can be acquired perinatally or through sexual contact, blood transfusion, needlestick, and needle sharing.
- **Hepatitis G** has been identified in a small number of patients through screening of the blood supply but has not yet been associated with clinical disease.
- **Hepatitis B and C** can lead to a chronic form, which can cause cirrhosis and hepatocellular carcinoma.

Note

Four million people in the United States are infected with hep C. Hep C is the most common disease requiring liver transplantation.

All forms can occasionally present with fulminant hepatic necrosis and acute liver failure.

The most common presentation of acute hepatitis of any cause is jaundice, dark urine, light-colored stool, fatigue, malaise, weight loss, and a tender liver. On physical examination the liver may be enlarged.

You cannot distinguish the precise viral etiology of the hepatitis by initial presentation alone. In fact, drug-induced hepatitis, i.e., that from isoniazid or massive alcohol use, may present with the same symptoms. Hepatitis B and C can also produce symptoms similar to serum sickness, such as joint pain, rash, vasculitis, and glomerulonephritis. They also lead to cryoglobulinemia. Hepatitis B has been associated with the development of polyarteritis nodosa (PAN). Hepatitis E has been associated with a more severe presentation in pregnant women.

Table 7-4. Comparative Features: Hepatitis A, B, C, E, and Delta

Feature	Hepatitis A	Hepatitis B	Hepatitis C	Delta	Hepatitis E
Incubation period (wk)	2–6 (avg. 4)	4–26 (avg. 13)	2–20	4–8	—
Transmission	Fecal-oral	Sexual > parenteral	Parenteral > sexual	Parenteral, sexual	Fecal-oral
Severity	Mild	Occasionally severe	Usually subclinical	Co-infection with B	Mild, except in pregnant women
Fulminant hepatitis	Rare	Very rare (1% of icteric patients	Extremely rare	Co-infection occasional	Rare
Symptoms	Fever, malaise, headache, anorexia, vomiting, dark urine, jaundice	As with A, but 10–20% with serum sickness-like (joint pain, rash)	Only 20% acutely symptomatic	As with A	As with A
Carrier state	None	Yes	Yes	Yes	None
Chronicity (%)	0	5–10	80	5	0
Associated with blood transfusion (%)	Very rare	5–10	Almost negligible 2% to routine screening	Occurs, but frequency unknown	Rare
Serology	Anti-HAV IgM fraction IgG fraction	HBsAg, HBsAb HBeAg Anti-HBs Anti-HBc Anti-HBe	Antibody to hepatitis C PCR-RNA	Anti-delta IgM fraction IgG fraction	Anti-Hep E IgM IgG
Postexposure prophylaxis	Immunoglobin Hep A vaccine	HBIg/Hep B vaccine	None effective	None	Unknown
Association with cirrhosis	No	Yes	Yes	Yes	No
Association with primary hepatocellular carcinoma	No	Yes	Yes	Yes	No

Diagnosis. All forms of viral and drug-induced hepatitis will produce elevated total and direct bilirubin levels.

- Viral hepatitis will produce both elevated ALT and AST, but ALT is usually greater than the AST.
- With drug- and alcohol-induced hepatitis, AST is usually more elevated than the ALT.
- Alkaline phosphatase and GGTP are less often elevated because these enzymes usually indicate damage to the bile canalicular system or obstruction of the biliary system.
- If there is very severe damage to the liver, prothrombin time and albumin levels will be abnormal.

Note

For the treatment of hepatitis B, entecavir, adefovir, tenofovir, and telbivudine can be used in place of lamivudine.

Hepatitis A, C, D, and E are diagnosed as **acute** by the presence of the IgM antibody to each of these specific viruses. IgG antibody to hepatitis A, C, D, and E indicates old, resolved disease.

- Hepatitis C activity can be followed with PCR-RNA viral load level. However, do not use PCR to establish the initial diagnosis.
- Hepatitis B is diagnosed as acute with the presence of the hepatitis B surface antigen, which is the first viral marker to elevate. The hepatitis B e antigen and IgM core antibody also help establish acute infection.
  - The e antigen indicates high levels of viral replication and is a marker for greatly increased infectivity.
  - Resolution of the infection is definitively indicated by the loss of surface antigen activity and the development of hepatitis B surface antibody.
  - Hepatitis B core antibody of the IgG type and hepatitis e antibody also indicate that the acute infection is about to resolve and may be the only marker present in the 2–6 weeks between the loss of surface antigen activity and development of the surface antibody.

Treatment. There is no effective treatment for acute hepatitis B. For chronic hepatitis B, treatment is interferon, entecavir, or tenofovir. (See GI section for indications for treatment.)

With the approval of the newest hepatitis C drugs, the goal of HCV treatment is to cure the virus, which can be done with a combination of drugs. The specific medications used and the duration of treatment depend on a number of factors:

- HCV genotype
- Viral load
- Past treatment experience
- Degree of liver damage
- Ability to tolerate the prescribed treatment
- Whether patient is waiting for a liver transplant or is transplant recipient

There are a number of approved therapies to treat HCV, such as sofosbuvir/ledipasvir, simeprevir, sofosbuvir, and Viekira Pak (ombitasvir, paritaprevir and ritonavir tablets co-packaged with dasabuvir tablets that may be prescribed with or without ribavirin). Simeprevir and sofosbuvir can be prescribed together with or without ribavirin, or each may be separately combined with ribavirin and in some cases peginterferon as well.

Sofosbuvir/ledipasvir, the current preferred HCV treatment, is 2 drugs formulated in to one daily pill. For genotype 1 success rates of sofosbuvir/ledipasvir are around 94–99%, while treatment duration is 8–12 weeks. Both are direct-acting antivirals which means they directly interfere with hepatitis C virus replication. Sofosbuvir is a polymerase inhibitor, while ledipasvir is an NS5A inhibitor. Patients who have never been treated for HCV—whether they have cirrhosis or not—take sofosbuvir/ledipasvir for 12 weeks. Treatment-naïve patients without cirrhosis whose pre-treatment viral load (HCV RNA) is <6 million IU/mL may be considered for **8 weeks of treatment**.

When hepatitis C treatment is working, the virus will become undetectable within 4–12 weeks and will remain that way throughout treatment. Patients are considered cured when they have achieved what is known as a sustained virologic response (SVR), or continuation of this undetectable status, 12–24 weeks after completing therapy.

After a needlestick from a hepatitis B surface-antigen–positive patient, the person stuck should receive hepatitis B immunoglobulin (HBIg) and hepatitis B vaccine. If the person stuck already has protective levels of surface antibody to hepatitis B present in the blood, then no further therapy is indicated. There is no effective postexposure prophylaxis to hepatitis C, and there is no vaccine. All healthcare workers, IV drug users, and others at risk should be vaccinated for hepatitis B. All newborn children are vaccinated against hepatitis B and A. Hepatitis A vaccine should be given to those traveling to countries that may have contaminated food and water, those with chronic liver disease, and those with high risk sexual behavior.

Clinical Recall

Which of the following hepatitis B markers indicates a high level of infectivity?

A. HBsAg

B. HBeAg

C. HBcAg

D. HBcAg IgM

E. HBcAg IgG

Answer: B

GENITAL AND SEXUALLY TRANSMITTED INFECTIONS

Urethritis

A 31-year-old man is in your clinic today with several days of urinary frequency, urgency, and burning.

Note

Check for terminal compliment deficiency in recurrent *Neisseria* infection.

Urethritis is inflammation of the urethra.

- Gonococcal urethritis caused by *Neisseria gonorrhoeae*
- Nongonococcal urethritis caused by *Chlamydia trachomatis* (50%), *Ureaplasma urealyticum* (20%), *Mycoplasma hominis* (5%), *Trichomonas* (1%), or herpes simplex

Symptoms include purulent urethral discharge, dysuria, urgency, and frequent urination. Disseminated gonococcal infection can cause purulent arthritis alone or arthritis-dermatitis with any of the following:

- Peripheral necrotic pustules, including palms and soles
- Monoarthritis or oligoarthritis
- Tendon sheath inflammation

NAAT of the urine or urethral swabs from men (vagina or cervix from women) is the best test.

Treatment. Single-dose ceftriaxone intramuscularly and single-dose azithromycin orally is the treatment of choice. An alternative regimen with doxycycline for 7 days can also be used.

- Treatment for gonorrhea is single-dose cefixime (same treatment as cervicitis); do not use ciprofloxacin as first-line therapy for gonorrhea.
- Treatment for disseminated gonococcal infection is 7–14 days of ceftriaxone.

Pelvic Inflammatory Disease

Pelvic inflammatory disease (PID) is a group of infections involving the fallopian tubes, uterus, ovaries, or ligaments of the uterus. The etiology is *N. gonorrhoeae*, *Chlamydia*, *Mycoplasma*, anaerobic bacteria, or gram-negative bacteria. Intrauterine devices predispose to PID.

Clinical findings include lower abdominal and pelvic pain on palpation of the cervix, uterus, or adnexa; fever, leukocytosis, and discharge are common. **Uterine, adnexal or cervical motion tenderness** is key. Discharge from the cervix may be present.

To diagnose *N. gonorrhoeae* and chlamydia trachomatis, order a NAAT.

- If there is fluid in the retrouterine cul-de-sac, a culdocentesis is performed (rare).
- Do a pregnancy test.
- If no response to antibiotics, U/S of the pelvis may exclude other pathology, such as an ovarian cyst or tubo-ovarian abscess.
- Clinical presentation is the main method (CMT/adnexal tenderness).

Treatment.

- **Inpatient**: doxycycline and cefoxitin (or cefotetan); indications for treating inpatient include no improvement in 48–72 hours; nausea/vomiting; high fever; pregnancy; or abscess
- **Outpatient**: single-dose ceftriaxone intramuscularly and doxycycline (with or without metronidazole) orally for 2 weeks; alternatively, 2 weeks of oral ofloxacin, with metronidazole as a second-line agent

Complications of PID include infertility and ectopic pregnancy.

Syphilis

A 43-year-old man comes to the clinic with several days of an ulcerated genital lesion. He also has some surrounding adenopathy.

Syphilis is a systemic contagious disease caused by a spirochete; characterized by periods of active manifestations and by periods of symptomless latency. It is **caused by *Treponema pallidum***.

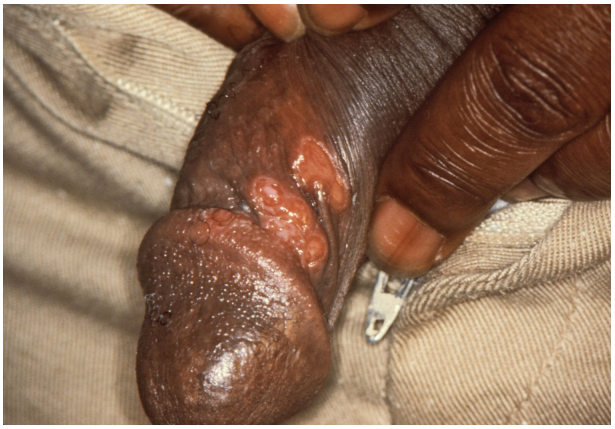
Syphilis can be classified as being congenital or acquired.

Congenital

- **Early:** symptomatic; seen in infants up to age 2
- **Late:** symptomatic, Hutchinson teeth, scars of interstitial keratitis, bony abnormalities (saber shins)

Acquired

- Early infectious syphilis
  - **Primary stage**: chancre appears by week 3 and disappears in 10–90 days; also, regional lymphadenopathy is painless, rubbery, discrete, and nontender to palpation (primary chancres are found on penis, anus, rectum [men], and vulva/cervix/perineum [women] but may appear on lips, tongue, etc.)
  - **Secondary stage**: cutaneous rashes appear 6–12 weeks after infection, usually found symmetrically and more marked on flexor and volar body surfaces (pinkish in white persons; pigmented spots/copper-colored macules in blacks); lymphadenopathy, papules which form at mucocutaneous junctions and moist areas, are called condylomata lata (extremely infectious), and alopecia can be seen
- **Latent stage**: asymptomatic; may persist for life; 35% of patients develop late or tertiary syphilis
- **Late or tertiary syphilis**: most commonly neurologic



Centers for Disease Control and Prevention, M. Rein, VD

Figure 7-5. Syphilis, Primary Chancre

Patients are symptomatic but not contagious.

- Benign tertiary syphilis develops 3–20 years after the initial infection; typical lesion is the gumma (a chronic granulomatous reaction) found in any tissue or organ, which will heal spontaneously and leave a scar
- Cardiovascular (aortitis) syphilis and neurosyphilis are the other manifestations of tertiary syphilis.
  - The Argyll Robertson pupil (usually only with neurosyphilis) is a small irregular pupil that reacts normally to accommodation but not to light.
  - Tabes dorsalis (locomotor ataxia) results in pain, ataxia, sensory changes, and loss of tendon reflexes.
  - Neurosyphilis is rare and is essentially the only significant manifestation of tertiary syphilis likely to be seen.

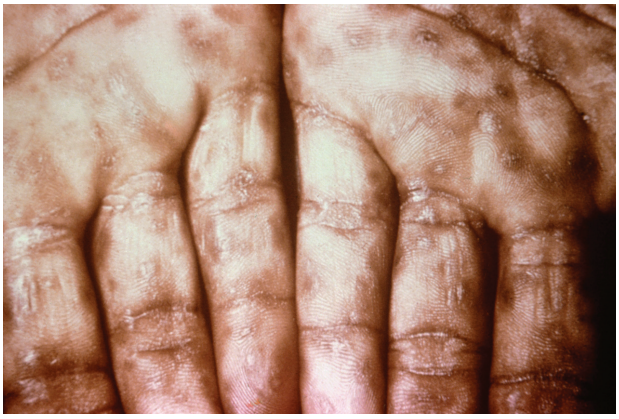


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Figure 7-6. Syphilis, Secondary Palms

Diagnosis.

- Screening tests are the VDRL and RPR.
  - VDRL and RPR should decrease in titers or become negative after treatment and increase if reinfected.
- Specific tests are the FTA-ABS, treponema pallidum particle agglutination (TPPA) assay, MHA-TP (microhemagglutination assay for *T. pallidum*), and Darkfield exam of chancre.
  - FTA-ABS and MHA-TP antibodies will remain positive indefinitely.
- VDRL with EBV, collagen vascular disease, TB, and subacute bacterial endocarditis can all have false-positives.
- Diagnosis of neurosyphilis is made if **any of the following** are present:
  - CSF lymphocytes >5/uL
  - Elevated CSF protein
  - Positive CSF VDRL
- CSF examination to confirm neurosyphilis and to confirm any neurological signs/symptoms in primary or secondary syphilis

Treatment. Penicillin is the **drug of choice** for all stages of syphilis.

- Primary, secondary, and latent syphilis are treated with 2.4 million units of intramuscular benzathine penicillin given 1×/week.
  - Primary and secondary syphilis (and early latent, e.g., <1 year) receive 1 week of therapy.
  - Late latent syphilis and tertiary nonneurosyphilis receive 3 weeks of therapy (and are diagnosed when VDRL or RPR titers are elevated >1:8 without symptoms).
  - Neurosyphilis receives 10–14 days of IV penicillin, with 10–20 million units per day.
- Those with penicillin-allergy receive doxycycline for primary and secondary syphilis, but must be desensitized for neurosyphilis. Pregnant patients must also undergo desensitization.

Caution that a reaction called Jarisch-Herxheimer can occur in >50% of patients a few hours after starting penicillin treatment. Symptoms include malaise, fever, headache, sweating rigors, and temporary exacerbations of the syphilitic lesions.

Chancroid

Chancroid is an acute, localized, contagious disease characterized by painful genital ulcers and suppuration of the inguinal lymph nodes. It is caused by *Haemophilus ducreyi* (gram-negative bacillus).

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Figure 7-7. Chancroid Lesion

Patients present with small, soft, painful papules that become shallow ulcers with ragged edges. They vary in size and coalesce. Inguinal lymph nodes become very tender and enlarged.

Diagnosis is made on clinical findings; do a Gram stain initially with culture to confirm. PCR testing is useful. Treatment is azithromycin single dose or ceftriaxone intramuscularly (single dose). Alternatives include erythromycin for 7 days or ciprofloxacin for 3 days.

Lymphogranuloma Venereum

Lymphogranuloma venereum is a contagious, sexually transmitted disease having a transitory primary lesion followed by suppurative lymphangitis. It is caused by *Chlamydia trachomatis.*

Clinical findings include the following:

- Small, transient, nonindurated lesion that ulcerates and heals quickly
- Unilateral enlargement of inguinal lymph nodes (tender)
- Multiple draining sinuses (buboes) that develop (purulent or bloodstained)
- Scar formation, persistent sinuses; fever, malaise, joint pains, and headaches (all common)

Diagnosis is made by clinical examination, history, and a high or rising titer of complement fixing antibodies. Isolate chlamydia from pus in buboes. Treat with doxycycline or erythromycin.

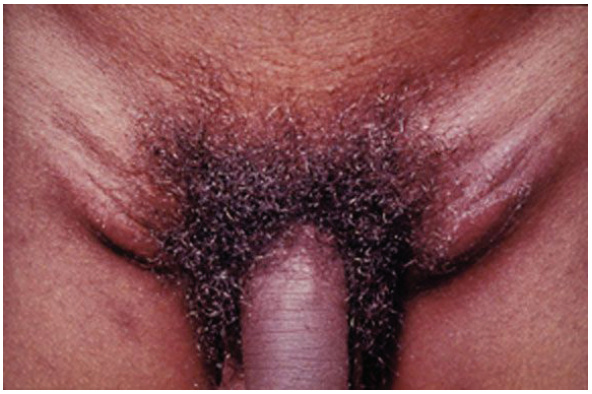

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Figure 7-8. Lymphogranuloma Venereum

Granuloma Inguinale

Granuloma inguinale is a chronic granulomatous condition, probably spread by sexual contact. It is caused by Donovania granulomatis *Calymmatobacterium granulomatis.*

A painless, red nodule will develop into an elevated granulomatous mass. In men, it is seen on the penis, scrotum, groin, and thighs. (In homosexual men, the anus and buttocks are common areas.) In women it is found on the vulva, vagina, and perineum.

Healing is slow, and there is scar formation. It looks like condyloma lata or carcinoma.

Diagnosis is made clinically and by performing a Giemsa or Wright stain (Donovan bodies) or smear of lesion. Also do punch biopsy. Treat with doxycycline, ceftriaxone, or TMP/SMZ. Erythromycin is an alternative.

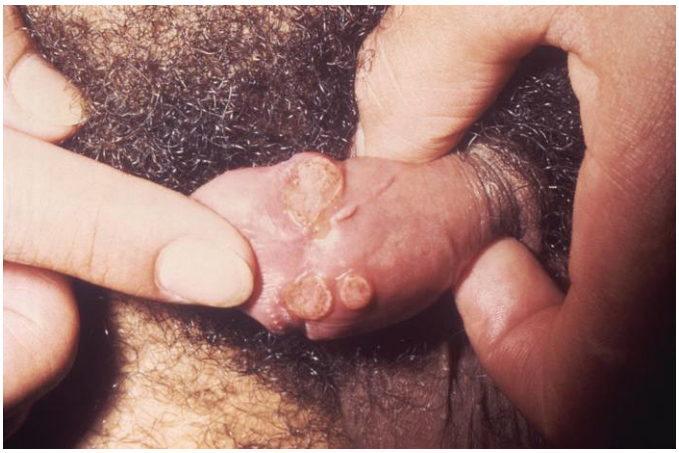

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Figure 7-9. Lesions of Granuloma Inguinale Due to *Calymmatobacterium Granulomatis* Infection

Genital Herpes

Genital herpes is generally the **herpes virus type II**, although type I may be seen. Vesicles develop on the skin or mucous membranes; they become eroded and painful and present with circular ulcers with a red areola. Itching and soreness usually precede them. Lesions are commonly seen on the penis (men) and on the labia, clitoris, perineum, vagina, and cervix (women).

The ulcers are scarring and there can be inguinal lymphadenopathy.

- Diagnosis is made with the direct fluorescent antibody test or HSV PCR obtained from the ulcers. Tzanck test and culture are no longer used.
- Serology is not useful for diagnosing herpes infections.
- Treat with oral acyclovir, famciclovir, or valacyclovir. Make sure to educate the patient about the relapsing nature of the disease. Those with frequent recurrence should be given chronic suppressive therapy.
- Foscarnet is used for resistant herpes.

Genital Warts

Genital warts are also known as condylomata acuminata or venereal warts. They are caused by the papilloma virus.

Genital warts are commonly found on warm, moist surfaces in the genital areas. They appear as soft, moist, minute, pink, or red swellings which grow rapidly and become pedunculated. Their cauliflower appearance makes them unique in appearance.

Clinical Correlate

Transmission of genital herpes commonly occurs during an **asymptomatic phase**, when a person who is shedding the virus inoculates virus onto a mucosal surface of the sexual partner.

Note

Erythema multiforme is most commonly caused by HSV recurrences.

Diagnosis is made by clinical appearance. Differentiation must be made between flat warts and condylomata lata of secondary syphilis. Treatment includes the following:

- Destruction (curettage, sclerotherapy, trichloroacetic acid)
- Cryotherapy
- Podophyllin
- Imiquimod (an immune stimulant)
- Laser removal

Clinical Recall

Which of the following is the treatment of choice for tertiary syphilis?

A. IM penicillin G x 1 dose

B. PO doxycycline x 14 days

C. IV penicillin G x 10 days

D. Doxycycline x 28 days

E. IV ceftriaxone x 1 day

Answer: C

URINARY TRACT INFECTIONS

Cystitis

A 32-year-old woman presents with dysuria. For the last several days, she has had burning on urination with increased frequency and urgency to urinate.

Cystitis is infection of the urinary bladder. It is very common, mostly in women. In the United States, it causes 6 million office visits each year.

Note

Screen for and treat asymptomatic bacteriuria only in those who are pregnant or about to undergo an invasive urologic procedure.

Etiology.

- Roughly the same as for pyelonephritis
- Any cause of urinary stasis or any foreign body predisposes
- Tumors/stones/strictures/prostatic hypertrophy/neurogenic bladder
- Sexual intercourse in women ("honeymoon cystitis")
- Catheters are a major cause, and the risk is directly related to the length of catheterization (3–5% per day).
- Microbiology: *E. coli* in >80%; second are other coliforms (gram-negative bacilli) such as *Proteus*, *Klebsiella*, *Enterobacter*, etc.; enterococci occasionally, and *Staph. saprophyticus* in young women.

Common presenting symptoms include dysuria, frequency, urgency, and suprapubic pain. Hematuria is less common. On exam, there is suprapubic tenderness but no flank tenderness.

Diagnosis

- Urinalysis (most important test) looking for WBCs >10 or urine dipstick positive for leukocyte esterase and nitrites
- Nitrites are indicative of gram-negative infection.
- Complicated UTI is UTI with co-morbid conditions, e.g., DM, pregnancy, kidney transplant, stones or anatomic abnormality, catheterization, recent antibiotics, or recent hospitalization. UTI in males is also considered complicated.
- Urine culture with >100,000 colonies of bacteria per mL of urine confirmatory but not always necessary with characteristic symptoms and a positive urinalysis. Obtain cultures if complicated UTI, recurrent UTI, or patient is pregnant.

Treatment

- For **uncomplicated cystitis**, 3 days of TMP/SMZ, 5 days of nitrofurantoin, or 1 dose of fosfomycin. Do not use quinolones.
- For **complicated cystitis**, check cultures and give fluoroquinolones for 7–14 days. For pregnancy, give amoxicillin-clavulanate, nitrofurantoin, cefpodoxime, or cefixime for 7 days and check culture after treatment. Do not use TMP/SMZ if used in the last 3 months.
- For **recurrent UTI**, give antibiotic prophylaxis either postcoital or daily.

Acute Bacterial Pyelonephritis

Acute bacterial pyelonephritis is an acute patchy, most often unilateral, pyogenic infection of the kidney. Infection usually occurs by ascension after entering the urethral meatus.

- Predisposing factors include obstruction due to strictures, tumors, calculi, prostatic hypertrophy, or neurogenic bladder, vesicoureteral reflux
- Women > men
- More common in childhood, during pregnancy, or after urethral catheterization or instrumentation
- *E. coli* is most common pathogen; others include *Klebsiella*, *Proteus*, and *Enterococcus*
- Patients who are immunosuppressed and subjected to indwelling catheters are more prone to *Candida*.

Pathology shows polymorphonuclear neutrophils and leukocytes (in interstitial tissue and lumina of tubules). Clinical findings include chills, fever, flank pain, nausea, vomiting, costovertebral angle tenderness, increased frequency in urination, and dysuria.

Diagnose with fever, dysuria, and flank pain. Confirm with clean-catch urine for urinalysis, culture, and sensitivity. In most cases, **>100,000 bacteria/mL of urine**.

Routine imaging is not required, but if there is no improvement in 48–72 hours or complications are suspected (obstruction, renal, or perinephric abscess), consider U/S or CT.

Note

- Ceftazidime-avibactam can be used for ESBL and carbapenem-producing gram negatives.
- Ceftolozane-tazobactam and colistin can be used for multi-drug resistant *Pseudomonas*.

Note

Any of the antibiotics for gram-negative bacilli are effective for acute bacterial pyelonephritis.

Treatment is antibiotics. Fluoroquinolone, piperacillin-tazobactam (a carbapenem), a third-generation cephalosporin (ceftriaxone), or cefepime are all acceptable.

- If **uncomplicated**: 5–7 days
- If **complicated**: 14 days
- Do not use nitrofurantoin, as its effectiveness has been proven only in the lower urinary tract.
- Do not use TMP/SMZ for empiric therapy until culture results and antibiotic sensitivity results are available, because of its increasing resistance throughout the United States.

Most patients can be treated as outpatients, though pregnant women who appear very ill and those unable to tolerate oral medication due to nausea or vomiting should initially be hospitalized.

ESBLs producing *E. coli* and Klebsieilla are becoming more and more common. Required treatment is a carbapenam.

Perinephric Abscess

Perinephric abscess is a collection of infected material surrounding the kidney and generally contained within the surrounding Gerota fascia. It is very uncommon. Although any factor predisposing to pyelonephritis is contributory, stones are the most important and are present in 20–60%. Other structural abnormalities, recent surgery, trauma, and diabetes are also important.

Pathophysiology

- Arises from contiguous pyelonephritis that has formed a renal abscess
- Rupture occurs through the cortex into the perinephric space
- Microbiology: *1*) The same coliforms as in cystitis and pyelonephritis; *2*) *E. coli* most common, then *Klebsiella*, *Proteus*; *3*) *Staph. aureus* sometimes accounts for hematogenous cases

Signs and Symptoms

- Often insidious; 2–3 weeks of symptoms prior to first physician visit
- Fever is the most common symptom
- Flank pain/palpable abdominal mass/abdominal pain
- Persistence of pyelonephritis-like symptoms despite treatment for pyelonephritis

The best initial tests are urinalysis (normal 30%) and urine culture (normal 40%). Fever and pyuria with negative urine culture or polymicrobial urine culture are suggestive.

Imaging is essential; U/S is the best initial scan but CT or MRI scan offers better imaging. Aspiration of the abscess is needed for definitive bacteriologic diagnosis (should be done if still febrile after 72 hours of antibiotics).

Treatment.

- Antibiotics for gram-negative rods
- Third-generation cephalosporins, antipseudomonal penicillin, or ticarcillin/clavulanate, often in combination with an aminoglycoside, for example
- Antibiotics alone are unlikely to be successful. Drainage (usually percutaneous) is necessary.

BONE AND JOINT INFECTIONS

Osteomyelitis

A 59-year-old man was admitted last night because of a painful leg for 2 weeks. Over the last 4 days, he developed an ulcer over the proximal portion of his tibia just below the knee. He has a history of peripheral vascular disease and diabetes. He is afebrile. He has a sinus tract in the center of the red, inflamed ulcer that is draining purulent material.

Osteomyelitis is an infection of any portion of the bone including marrow, cortex, and periosteum. There are 3 types:

- **Acute hematogenous** occurs mostly in children in the long bones of the lower extremities and is secondary to a single organism 95% of the time.
  - Most common organism is *Staphylococcus aureus*
  - Most commonly involved bones are tibia and femur
  - Most commonly involved location is metaphyseal due to the anatomy of the blood vessels and endothelial lining at the metaphysis
  - In adults, hematogenous osteomyelitis accounts for about 20% of all cases and the most common site is the vertebral bodies (lumbar vertebrae are most frequently involved)
  - The infection can extend posteriorly to form an epidural abscess; a patient with this diagnosis would present with fever and back tenderness.
- **Secondary to contiguous infection** can occur in anyone with recent trauma to an area or placement of a prosthetic joint. Although this is secondary to a single organism most of the time, a higher percentage is polymicrobial in origin. *S. aureus* is the most common organism.
- **Vascular insufficiency** is mostly seen age >50, with diabetes or peripheral vascular disease, resulting in repeated minor trauma that is not noticed because of neuropathy and decreased sensation. It is most common in small bones of the lower extremities. The majority is polymicrobial, but the single most common organism is still *S. aureus*.

Clinical Presentation. Pain, erythema, swelling, and tenderness over the infected bone. With vascular insufficiency, there is often an obvious overlying or nearby ulceration or wound. Occasionally, a draining sinus tract is present.

Note

Injection drug use is a significant risk factor for vertebral osteomyelitis in adults.

Note

In general, nuclear medicine studies are less sensitive and specific.

Diagnosis. The earliest tests to detect osteomyelitis are the CT scan and MRI.

- Plain x-ray (**usually the initial test** because so easily obtained and inexpensive)
  - First visible abnormality will be a periosteal elevation
  - However, 50–75% of bone calcification must be lost before the bone itself appears abnormal, which usually takes at least 2 weeks to develop.
- MRI if x-ray is negative; if not available, do a CT with IV contrast
- ESR: nonspecific, but useful to follow during treatment; a normal value strongly points away from osteomyelitis
- Bone biopsy and culture: essential to confirm the pathogen and choose antibiotic therapy; not needed if blood cultures are positive

Treatment.

- **Acute** hematogenous osteomyelitis in **children**: antibiotics alone
- Osteomyelitis in **adults**: antibiotics + surgery (wound drainage and debridement, removal of infected hardware)
- **Chronic** osteomyelitis: antibiotics for up to 12 weeks or even longer
- Antibiotic therapy depends on the specific isolate obtained, which must be as precise as possible because empiric treatment for 4–6 weeks would be undesirable.
- Antibiotics should be held until cultures return. Start empiric antibiotics (imipenem and vancomycin) only if patient is unstable.
- The other MRSA drugs are daptomycin, linezolid, ceftaroline, and tigecycline.

Septic Arthritis

A 73-year-old woman presents with a swollen right knee for several days. The knee has an obvious effusion and decreased mobility. There is also redness and tenderness of the knee.

Septic arthritis is an infection of a joint due to virtually any agent. The most common etiology is bacterial; specifically, *Neisseria gonorrhoeae*, staphylococci or streptococci, but *Rickettsia*, viruses, spirochetes, etc., may also cause it. Generally, bacterial arthritis is divided into gonococcal and nongonococcal types.

Pathogenesis. Sexual activity is the only significant risk factor for gonococcal septic arthritis. A total of 1–5% of people with gonorrhea will develop disseminated disease, and 25% will have a history of recent symptomatic gonorrhea. Nongonococcal bacterial arthritis is usually spread by the hematogenous route. Additional routes may include bites (animal or human), direct inoculation of bacteria into the joint through surgery or trauma, or spread of infection from surrounding structures such as bone. Even though both normal or damaged joints can get infected, any previous damage to a joint, such as from rheumatoid arthritis or osteoarthritis, previous surgery, prosthesis placement, gout, sickle cell disease, or the presence of certain risk factors such as IV drug abuse, diabetes mellitus, or HIV infection can predispose a joint to infection. Any cause of bacteremia can seed the joint because the synovium does not have a basement membrane.

Microbiology. Nongonococcal:

- Gram-positive (>85); (*S. aureus* [60%], *Streptococcus* [15%], *Pneumococcus* [5%])
- Gram-negative (10–15%)
- Polymicrobial (5%)

Presentation includes the following:

- **Nongonococcal:** monoarticular in >85%, with a swollen, tender, erythematous joint with a decreased range of motion (knee most common); skin manifestations rare
- **Gonococcal:** polyarticular in 50%; a tenosynovitis is much more common (effusions less common; migratory polyarthralgia common; skin manifestations with petechiae or purpura common)

Diagnosis

- **Nongonococcal.** Culture of joint aspirate fluid is positive in 90–95% and Gram stain is positive in 40–70%. Cell count of synovial fluid is high (>50,000) and is predominantly PMNs with a low glucose. Blood culture is positive in 50%.
- **Gonococcal.** Much harder to culture. Only 50% of joint aspirates have positive synovial fluid culture; <10% of blood cultures are positive. Other sites such as cervix, pharynx, rectum, and urethra may also be positive. In the aggregate, culture of the other sites has a greater yield than culturing the joint itself.

Treatment. Bacterial arthritis is usually treated by a combination of joint aspiration and antimicrobial therapy.

- **Nongonococcal.** In the absence of a specific organism seen on a stain or obtained from culture, good empiric coverage is vancomycin to cover MRSA. Add ceftriaxone or another third-generation cephalosporin for gram-negative coverage if the patient is immunocompromised or with joint trauma.
- **Gonococcal.** Ceftriaxone is the drug of choice.

Gas Gangrene (Clostridial Myonecrosis)

Gas gangrene is the necrotizing destruction of muscle by gas-producing organisms, associated with signs of sepsis. It is largely caused by the spread of infection from wounds contaminated by *Clostridium perfringens* (the toxins produced by clostridia play a significant role in tissue damage). It is strongly associated with traumatic injury (50%), shrapnel in war, and motor vehicles in peacetime. The trauma may be as minor as an intramuscular injection; however, the wound must be deep, necrotic, and without exit to the surface. Postoperative (30%), nontraumatic (20%).

Symptoms usually begin <1–4 days of incubation after the wound; they include pain, swelling, and edema at the site of the wound. Later hypotension, tachycardia, and fever can occur. Crepitation over the site and renal failure are late developments, usually prior to death.

Diagnosis. A Gram stain of the wound shows gram-positive rods, but no white cells. A culture may be positive for *C. perfringens* as early as 1 day; however, this is not necessarily diagnostic because up to 30% of wounds can be colonized by *Clostridia*. Gas bubbles on x-ray are suggestive but may be caused by streptococci as well. Direct visualization (usually at surgery) of pale, dead muscle with a brownish, sweet-smelling discharge is ultimately diagnostic.

Note

Gas gangrene is not common; a large referral center may admit 10 cases per year. However, incidence increases during times of war.

Note

In the past, uterine gangrene was a major complication of improper abortion.

Treatment. High-dose penicillin (24 million/day) and clindamycin (if penicillin allergic) is necessary, but surgical debridement or amputation is the absolute center of treatment.

Hyperbaric oxygen may help, but that is still controversial.

Clinical Recall

What is the most appropriate treatment for gas gangrene?

A. High-dose penicillin
B. Clindamycin
C. High-dose penicillin and hyperbaric oxygen
D. IV doxycycline and surgical debridement
E. High-dose penicillin and surgical debridement

Answer: E

VECTOR-BORNE DISEASES

Malaria

- For prophylaxis, use mefloquine or atovaquone/proguanil (avoid mefloquine with history of neuropsychiatric illness)
- Treat with mefloquine or atovaquone/proguanil (for *Plasmodium falciparum*)
- Treat with chloroquine or primaquine (vivax and ovale only) (for non-*falciparum*)
- If severe, treat with artemisinin, not quinine

Dengue

Dengue is transmitted by mosquitos. Clinical presentation includes bone pain (back) and retro-orbital headache.

Symptoms also include severe thrombocytopenia, leukopenia, and transaminitis.

Chikungunya

Chikungunya is transmitted by mosquitos. Clinical presentation includes severe joint pain.

Lyme Disease

A couple presents to your office after a recent camping trip. The woman has found a tick bite but has had no symptoms. The man had a red skin lesion which resolved and was followed by the onset of facial palsy. He does not recall having sustained a tick bite.

Lyme disease is spread by the bite of the *Ixodes scapularis* (dammini) tick. On the basis of animal studies we know that the tick needs at least 24 hours of attachment to transmit the *Borrelia burgdorferi* organism. The tick is small, and the bite is often not remembered.

Symptoms begin 3–30 days after the bite of the tick.

- Erythema migrans rash at the site of the bite (80% of patients)
  - An erythematous patch, which may enlarge in the first few days, may have partial central clearing, giving it a "bull's-eye" appearance, although this is not commonly seen.
  - The rash will resolve in several weeks, even without treatment.
- Flulike illness with fever, chills, and myalgias (50% of patients)
- Neurologic symptoms several weeks later (10–20% of patients)
  - Paralysis of the seventh cranial nerve (facial paralysis) (**most common**), possibly bilateral
  - Meningitis, encephalitis, headache, and memory disturbance
- Cardiac symptoms (<10% of patients)
  - AV heart block (**most common**)
  - Myocarditis, pericarditis, and various forms of arrhythmias
- Joint involvement months to years later (up to 60% of patients)
  - A migratory polyarthritis
  - Chronic monoarticular arthritis (**most commonly affecting the knee**)

Diagnosis.

- Erythema migrans rash + at least one late manifestation
- Lab confirmation of the presence of the organism
- Serologic testing (**most commonly used test**)
  - ELISA test + a Western blot (**hallmark tests**)
  - The problem with serologic testing is that it often does not distinguish between current and previous infection.
  - Also, in early disease when patients have the rash, testing is often negative because patients have not had sufficient time to mount an immune response; in those situations, treatment should be given based on strong clinical suspicion, and serologic testing should not be done.
  - Serology will almost always be positive later in the course of the disease.

Treatment. Most patients are treated on the basis of the presence of the rash alone.

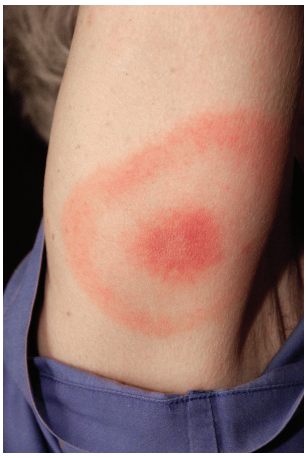
- Oral doxycycline for the rash, facial palsy, and joint pain
- Doxycycline or amoxicillin for minor symptoms
- IV ceftriaxone for more serious symptoms such as heart block, meningitis, myocarditis, or encephalitis

Note

When leukopenia and thrombocytopenia are seen with Lyme, think of co-infection with *Anaplasma phagocytophilum* and check a blood smear to evaluate for morulea.

Note

All cardiac and serious neurologic manifestations of Lyme should be treated with IV ceftriaxone.



Centers for Disease Control and Prevention, James Gathany

Figure 7-10. Erythema Migrans – Lyme Disease

Clinical Recall

Which of the following is an indication for prophylactic therapy in the management of infective endocarditis?

A. Congenital cyanotic heart lesions
B. Surgically corrected systemic pulmonary shunts
C. Hypertrophic cardiomyopathy
D. Mitral valve prolapse with valvular regurgitation
E. GI surgery

Answer: A

Rocky Mountain Spotted Fever

Rocky Mountain spotted fever (RMSF) is a bacterial infection caused by the organism *R. rickettsii.*

R. rickettsii is transmitted by the wood tick. The most common areas are the mid-Atlantic coast, upper South, and Midwest of the United States.

Clinical Findings.

- More common in spring and summer
- Triad: abrupt onset of fever, headache, and rash (erythematous maculopapules). This disease starts at wrist and ankles and spreads centripetally (can involve palms and soles).
- Differential diagnosis with syphilis

Symptoms include confusion, lethargy, dizziness, irritability, stiff neck, and GI symptoms. Rash starts by day 6.

Diagnosis is made with specific serology and a skin lesion biopsy. Treat with doxycycline.

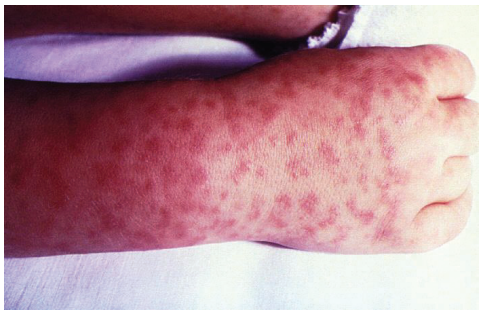


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Figure 7-11. Rash of Rocky Mountain Spotted Fever on an Infant

FUNGAL INFECTIONS

Aspergillosis

Aspergillosis is a fungus that is widespread in the environment; it primarily causes pulmonary disease in the immunocompromised.

- 90% species known, with *A. fumigatus* the most common
- Ubiquitous in natural decaying organic matter, ceiling tile, and ventilation systems
- Spores can be isolated from air anywhere on earth

Symptoms include:

- Various degrees of respiratory tract invasion
- Rarely it can disseminate to any organ but starts in the lung
- Allergic bronchopulmonary-like asthma with cough/fever/wheezing
- Mycetoma (a "fungal ball" that sets up residence in a pre-existing cavity [hemoptysis is chief complaint] but it is not invasive)
- Invasive pulmonary

Nearly 90% of patients have 2 of the following risk factors:

- Neutropenia <500
- History of steroid use
- History of cytotoxic drugs (e.g., azathioprine, cyclophosphamide)

Diagnosis.

- Abnormal chest x-ray and *Aspergillus* in sputum (all cases)
- Allergic bronchopulmonary elevation of allergy/asthma markers, such as eosinophil/IgE
- Positive skin testing
- Mycetoma: abnormal sputum culture/serum precipitins/x-ray
- Invasive disease (sputum culture not sufficient):
  - Biopsy needed to show invasion
  - CT scan (or chest x-ray) will show a "halo" sign, a zone of low attenuation around a nodular lesion (often an early finding in invasive pulmonary aspergillosis)
  - Positive galactomannan antigen test

Note

Voriconazole and caspofungin are used to treat aspergillosis and some other fungal infections.

Treatment. Depends on syndrome (really, they are separate diseases).

- Allergic: steroid taper and asthma medications, not antifungals
- Mycetoma: surgical removal
- Invasive: Voriconazole is superior to amphotericin; there are fewer failures seen with it (and caspofungin) as compared with amphotericin. Itraconazole for very mild disease or after initial treatment with amphotericin. Caspofungin is active against *Aspergillus* and may be superior to amphotericin. Caspofungin is an echinocandin. The other echinocandins are micafungin and anidulafungin. Echinocandins have virtually no toxicity.

Clinical Recall

Which of the following statements regarding HIV in pregnant women is correct?

A. A CD4 <200 is an indication for single treatment with AZT

B. Emtricitabine is contraindicated in pregnant women

C. C-sections are done when the viral load is >1000 copies/mL of HIV-RNA at the time of delivery

D. Treatment with HAART triple therapy is done only in women who are at high risk of transmitting the disease

E. Only give HAART triple therapy to pregnant patients with opportunistic infections

Answer: C

ENDOCARDITIS

A 40-year-old man with a history of IV drug use presents to the hospital with fever. On physical examination a systolic murmur at the lower left sternal border is noted.

Endocarditis is an infection of the endocardium, the inner lining of the heart chambers and valves. The heart valves are colonized with microbial organisms, causing friable infected vegetations and valve injury. Men > women.

Acute infective endocarditis is caused by bacteremia. *S. aureus* is the most common cause.

- Rapid onset with fever and sometimes sepsis
- Seed previously normal valves, producing necrotizing, ulcerative, invasive infection
- Produces large, bulky vegetations (2 mm to 2 cm) on the atrial side
- IV drug use a major risk factor
- Splenomegaly
- Associated with invasion of myocardium (abscess cavities) and rapid valve destruction
- Embolic complications, particularly to the lungs with right-sided lesions

Subacute infective endocarditis is commonly caused by viridans group streptococci. It is associated with low virulence.

- Slow onset with vague symptoms, leading to malaise, low-grade fever, weight loss, and flu-like symptoms
- Seed previously abnormal valves, producing smaller vegetations composed of fibrin, platelets, debris, and bacteria
- Risk factors include ventricular septal defect with shunt; stenosis of any valve; prosthetic valve; indwelling catheter; bicuspid aortic valve; mitral valve prolapse; and Marfan syndrome
- Destruction of valves

Bacterial endocarditis produces large vegetations and may affect any value in the heart, although left-sided lesions of the aortic and mitral valves are more common. Predisposing factors include dental procedures that cause bleeding; oral/upper respiratory tract/GU surgery; prosthetic heart valves; catheters in the right heart; pressure-monitoring catheters; and IV drug use.

Note

Subacute infective endocarditis is less fatal than acute endocarditis. With treatment, 5-year survival rate is almost 90%.

Table 7-5. Microorganisms Responsible for Infective Endocarditis

Organism	Incidence, %
Native valves	
Streptococcus viridans	50–60
Enterococci	5–15
Other streptococci:	15–20
Staphylococcus aureus	20–30
Staphylococcus epidermidis	1–3
Gram-negative bacilli	<5
Fungi (*Candida, Aspergillus, Histoplasma*)	<3
Culture negative	<5
In narcotic addicts	
Staphylococcus aureus	60–95
Staphylococcus epidermidis	5–10
Streptococci	10–20
Enterococci	8–10
Gram-negative bacilli	4–8
Fungi	4–5
Diphtheroids	1–2
Prosthetic valves	Acutely: first 2 months after surgery
Staphylococcus epidermidis	40–50 acutely; 10–20 later
Streptococcus viridans	5–20 acutely; 40–60 later
Staphylococcus aureus	15–20 acutely; 20–30 later
Enterococci	5–10
Other streptococci	1–5
Culture negative	<5

Table 7-6. Risk of Predisposing Conditions for Infective Endocarditis

High Risk	Intermediate Risk	Low/Negligible Risk
Prosthetic valves*	Mitral valve prolapse with regurgitation	Mitral prolapse without regurgitation
Aortic valve disease	Mitral stenosis	Atrial septal defect
Mitral regurgitation	Tricuspid valve disease	Luetic aortitis
Patent ductus arteriosus	Hypertrophic obstructive cardiomyopathy	Transvenous pacemakers
Arteriovenous fistula	Calcific aortic sclerosis Tetralogy of Fallot	Surgically corrected congenital lesions (no prosthesis) >6 mo after surgery
Coarctation of the aorta Indwelling right heart catheters (hyperalimentation)	Indwelling right heart and pulmonary artery catheters	Aortocoronary bypass surgery Cardiac pacemakers
Previous infective endocarditis	Nonvalvular intracardiac prosthesis	—
Marfan syndrome	—	—

*Indication for endocarditis prophylaxis

Clinical Manifestations.

Table 7-7. Incidence of Clinical Findings in Infective Endocarditis

Symptoms, %	Signs, %
Chills, 41	Heart murmur or changing murmur, 80–90
Weakness, 38	Fever, 90
Dyspnea, 36	Embolic events, 50
Sweats, 24	Skin manifestations, 50
Anorexia, weight loss, 24	Splenomegaly, 28
Malaise, 24	Septic complications, 19
Cough, 24	Mycotic aneurysms, 18
Skin lesions, 21	Glomerulonephritis, 10
Stroke, 18	Digital clubbing, 12
Nausea, vomiting, 17	Retinal lesions, 5
Chest pain, 16	

Table 7-8. Peripheral Manifestations of Infective Endocarditis

Physical Findings (Frequency)	Pathogenesis	Most Common Organisms
Petechiae (20–30%): red, nonblanching lesions in crops on conjunctivae, buccal mucosa, palate, extremities	Vasculitis or emboli	*Streptococcus, Staphylococcus*
Splinter hemorrhages (15%): linear, red-brown streaks most suggestive of IE when proximal in nailbeds	Vasculitis or emboli	*Staphylococcus, Streptococcus*
Osler's nodes (5–10%): 2–5 mm painful nodules on pads of fingers or toes	Vasculitis	*Streptococcus*
Janeway lesions (10–15%): macular, red, or hemorrhagic, painless patches on palms or soles	Emboli	*Staphylococcus*
Roth's spots (<5%): oval, pale, retinal lesions surrounded by hemorrhage	Vasculitis	*Streptococcus*

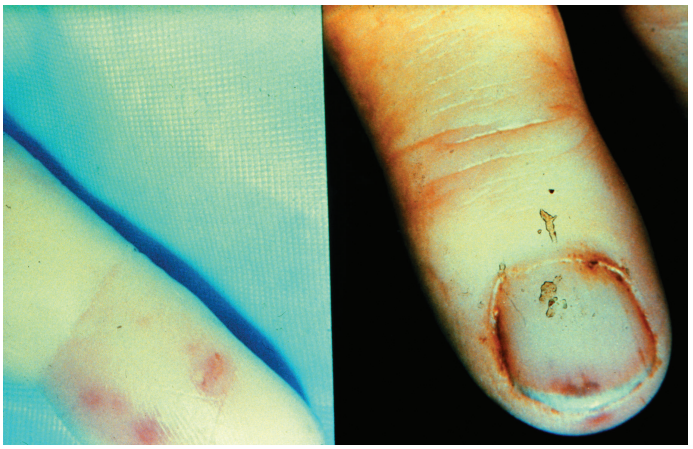

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Figure 7-12. Embolic Features of Acute Endocarditis

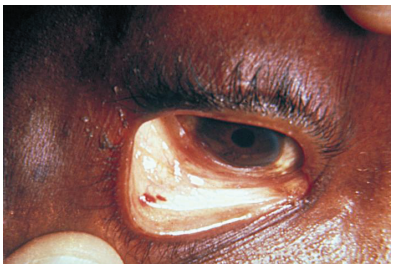

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Figure 7-13. Petechial Hemorrhage, an Embolic Phenomenon Due to Septicemia/Endocarditis

The following complications may be seen with infective endocarditis:

- CHF (**most common cause of death**)
- Septic embolization (related to infarctions and metastatic infections): brain ("mycotic" aneurysm); spleen (greater with subacute); kidneys; coronary arteries
- Glomerulonephritis with nephrotic syndrome or renal failure (immune complex)

Diagnosis. To diagnose endocarditis, **2 major criteria** are required: positive blood cultures and abnormal echocardiogram.

- Transthoracic echocardiogram has <60% sensitivity and excellent specificity.
- Transesophageal echocardiogram has >90% sensitivity and >95% specificity.

If 1 major criteria is absent, **1 major + 3 minor criteria** will constitute a diagnosis. The minor criteria are:

- Fever
- Predisposing cardiac lesion
- IV drug use
- Vascular phenomena (arterial embolic, septic pulmonary infarcts, Janeway lesions), immunologic phenomena (such as Osler nodes, Roth spots, glomerulonephritis, or a positive rheumatoid factor)
- Microbiologic evidence (positive blood cultures not meeting major criteria or evidence of active infection with an organism consistent with infective endocarditis)

Treatment is based on the organism found in blood culture and its specific antimicrobial sensitivities. If the patient is very ill or has heart failure and embolic phenomena, treatment can be started before the results come back. Acceptable empiric therapy is as follows:

- For **community-acquired native valve IE**: vancomycin or ampicliin-sulbactam + gentamicin
- For **nosocomial-associated IE**: vancomycin, gentamicin, rifampin and an antipseudomonal beta-lactam
- For **prosthetic valve IE**: vancomycin, gentamicin, and rifampin

As soon as the specific microbiologic agent is known, treatment must be altered.

Note

Always get at TEE in patients with *S. aureus bacteremia*.

Note

Look for colon cancer in patients with *Streptococcus bovis or Clostridium septicum* endocarditis.

Note

Coxiella burnetii can cause culture negative endocarditis. Think of this in patients exposed to large animals, such as farmers or zoo keepers.

Table 7-9. Treatment of Specific Microorganisms Causing Endocarditis

Organism	Medication	Duration
Strep. viridans	Penicillin	4 weeks
	Penicillin-allergic: ceftriaxone *or* vancomycin	4 weeks
	Penicillin or ceftriaxone + gentamicin	2 weeks
***Staph. aureus*, native valve** (Methicillin-sensitive)	Nafcillin (+ 5 days of gentamicin)	4–6 weeks
	Penicillin-allergic: cefazolin *or* vancomycin + gentamicin for first 5 days	4–6 weeks
(Methicillin-resistant)	Vancomycin	4–6 weeks
Enterococcal	Penicillin (or ampicillin) *and* gentamicin (vancomycin if penicillin-allergic)	4–6 weeks
	Penicillin-allergic or resistant: vancomycin *and* gentamicin	4–6 weeks

Surgery is required only in specific situations. The criteria for surgery in infective endocarditis are as follows.

Major criteria for surgery

- CHF, progressive or unresponsive to "simple" measures
- Recurrent systemic emboli
- Persistent bacteremia despite adequate antibiotic therapy
- Fungal etiology
- Extravalvular infection (atrioventricular block, purulent pericarditis)
- Prosthetic valve dehiscence or obstruction
- Recurrence of infection despite adequate therapy

Minor criteria for surgery

- CHF, resolved with medical therapy
- Single systemic embolic event
- Large aortic or mitral vegetations on echocardiography
- Premature mitral valve closure in acute aortic insufficiency
- Prosthetic valve infection due to organisms other than highly penicillin-sensitive streptococci
- Tricuspid endocarditis due to gram-negative bacilli
- Persistent fever without other identifiable cause
- New regurgitation in an aortic prosthesis

Prophylaxis

The number of cardiac lesions which are an indication for endocarditis prophylaxis has markedly diminished over the years. AS, MS, AR, and MR **no longer** need prophylaxis, even for dental procedures. Prophylactics are indicated when there is both a serious underlying cardiac defect and a procedure causing bacteremia.

- **Dental procedures**: amoxicillin; for penicillin-allergy, use clindamycin, azithromycin, clarithromycin, or cephalexin
- **Urinary or GI procedures:** prophylaxis no longer needed
- **Cardiac conditions that do require prophylaxis**:
  - Prosthetic cardiac valves, including bioprosthetic and homograft valves
  - Previous bacterial endocarditis, even in the absence of heart disease
  - Most congenital cardiac malformations, especially cyanotic lesions (negligible risk with isolated ASD) if **not** repaired
- **Anatomic conditions that do require prophylaxis**:
  - Prosthetic valves
  - Unrepaired cyanotic heart disease
  - Previous endocarditis
  - Valvulopathy following cardiac cardiac transplantation
  - Congenital heart defect repair with prosthesis or shunt done <6 months prior
- **Conditions that do not require prophylaxis**:
  - Surgically corrected systemic pulmonary shunts and conduits
  - Rheumatic and other acquired valvular dysfunction, even after valvular surgery
  - Hypertrophic cardiomyopathy
  - Mitral valve prolapse with valvular regurgitation
  - Surgically repaired intracardiac defects
- **Dental or surgical procedures that predispose to endocarditis**:
  - Dental procedures known to induce gingival or mucosal bleeding, including professional cleaning
  - Procedures that involve incision or biopsy of the respiratory mucosa
  - Tonsillectomy and/or adenoidectomy
  - Surgery to place prosthetic heart valves or prosthetic intravascular or intracardiac materials
  - Procedures on infected skin or tissue

Note

For the exam, prophylaxis for bacterial endocarditis is **high yield**.

ACQUIRED IMMUNE DEFICIENCY SYNDROME

Acquired immune deficiency syndrome (AIDS) is caused by the human immunodeficiency virus (HIV).

- Primary mechanism is infection of a subset of T lymphocytes called CD4 cells (or "T cells")
- Over time, HIV decreases the number of CD4 cells; as that happens, patient becomes at increased risk for opportunistic infections and certain malignancies
- Often a 10-year lag between contracting HIV infection and developing the first symptoms
  - CD4 cells drop at a rate of 50–100/μL/year without treatment
  - Would take 5–10 years to drop from normal CD4 count of 700/mm^3 to a count of 200/mm^3

Note

The mode of HIV acquisition varies around the world.

- In the United States, the primary mode is men having sex with men (MSM) and heterosexual intercourse (years ago, injection drug use played a larger role). For women, it is heterosexual transmission.
- In most developing nations, the primary mode is heterosexual transmission.

Opportunistic Infections in AIDS

Pneumocystis jirovecii (CD4 count <200/μL)

Clinical Presentation.

- Usually subacute onset and progression
- Pneumonia
- Dyspnea on exertion
- Dry cough
- Fever
- Chest pain

Diagnosis.

- Bronchoscopy with bronchoalveolar lavage for direct identification of the organism
- Chest x-ray will reveal bilateral, interstitial infiltrates
- Possible pneumothorax (chest x-ray may be normal)
- Moderately elevated LDH

Note

It is possible to have pneumocystis pneumonia (PCP) with a normal chest x-ray.

Treatment.

- TMP-SMZ (**first-line**) for mild to severe disease
  - May cause a rash
  - Can cause hyperkalemia, so do not combine with ACE inhibitors, ARBs, or spironolactone
  - Can inhibit the secretion of creatinine and cause a mild increase in creatinine (.05 mg/dL), but do not stop the medication as this is not a decrease in GFR
- Alternatively, combination treatment with one of the following:
  - Dapsone + trimethoprim
  - Primaquine + clindamycin
  - Leucovorin + atovaquone or trimetrexate

- Pentamidine for sulfa allergy: pancreatitis, hyperglycemia, hypoglycemia
- IV clindamycin + primaquine for sulfa allergy
- Steroids, as adjunct therapy for patients with severe pneumonia (i.e., PaO2 <70 mm Hg or A-a gradient >35 mm Hg)

Prophylaxis of PCP is as follows (in order of preference):

- TMP/SMZ orally (**most effective**)
- Dapsone
- Atovaquone
- Aerosolized pentamidine (**least effective**)

Prophylaxis may be discontinued if antiretrovirals raise CD4 >200/μL for >6 months.

Note

Severe pneumonia is defined as PaO2 <70 mm Hg or A-a gradient >35 mm Hg.

Cytomegalovirus (CD4 <50/μL)

Clinical Presentation.

- Retinitis: blurry/double vision, or any visual disturbance in a patient with very low CD4
- Colitis: diarrhea (<20% of patients)
- Esophagitis: odynophagia, fever, retrosternal chest pain (endoscopy reveals multiple shallow ulcers in the distal esophagus)
- Encephalitis: altered mental status, cranial nerve deficits

Diagnosis.

- Funduscopy for retinitis
- Colonoscopy with biopsy for diarrhea or upper GI endoscopy with biopsy of ulcers

Treatment.

- Valganciclovir to treat CMV retinitis (along with intravitreal ganciclovir) and GI manifestations of CMV disease
- IV ganciclovir for serious CNS infections and for those who cannot tolerate oral medications
- If no response or if ganciclovir-resistant, use foscarnet and cidofovir; note the following side effects
  - Ganciclovir can cause neutropenia or foscarnet-renal toxicity
  - Cidofovir can cause renal toxicity

Primary prophylaxis is not indicated. Valganciclovir is used for maintenance therapy.

Note

Valganciclovir, an oral prodrug of ganciclovir, achieves levels in the serum comparable to IV ganciclovir.

Mycobacterium avium complex (CD4 <50/μL)

Clinical Presentation.

- Ubiquitous atypical mycobacteria found in the environment
- Mode of infection is inhalation or ingestion
- Symptoms include fever, night sweats, bacteremia, wasting, anemia, diarrhea

Diagnosis.

- Blood culture
- Culture of bone marrow, liver, or other body tissue or fluid

Treatment.

- Clarithromycin + ethambutol +/– rifabutin
- Prophylaxis as follows:
  - Oral azithromycin 1×/week or clarithromycin 2×/day if CD4 <50/μL
  - May be discontinued if antiretrovirals raise CD4 >50/μL over a period of several months

Toxoplasmosis (CD4 <100/μL)

Clinical Presentation.

- Brain mass lesion
- Headache
- Confusion
- Seizures
- Focal neurologic deficits

Diagnosis.

- CT or MRI scan of the head will show several "ring" (contrast) enhancing lesions with edema and mass effect, usually in basal ganglia
- A trial of specific therapy is given for 2 weeks, and the scan is repeated; shrinkage of the lesions is considered diagnostic
- If there is no shrinkage, brain biopsy may be needed (rare)

Note

CNS lymphoma is usually one lesion (located in the periventricular region, periependymal area, or corpus callosum), whereas toxoplasmosis is multiple lesions.

Treatment.

- Pyrimethamine and sulfadiazine; if patient is sulfa-allergic, substitute clindamycin for sulfadiazine
- Leucovorin to prevent bone marrow suppression
- For prophlaxis: TMP/SMX; dapsone, pyrimethamine, and leucovorin; atovaquone +/– pyrimethamine

Cryptococcosis (CD4 <100/μL)

Clinical Presentation. Meningitis; patients mostly present with fever, headache, and malaise.

Diagnosis.

- Lumbar puncture with initial evaluation by India ink and then specific cryptococcal antigen testing. A lower CSF cell count implies worse disease.
- Serum cryptococcal antigen testing. A high antigen titer, high opening pressure, and low CSF cell count all imply a worse prognosis.

Treatment.

- IV amphotericin B for minimum 10–14 days (with flucytosine)
- Follow with oral fluconazole for maintenance and suppressive therapy; once CD4 >100/μL for 3 months, stop fluconazole
- Oral fluconazole is not recommended for general use as a prophylaxis. This is because the incidence of cryptococcal meningitis is too low to demonstrate a mortality benefit with its use.

Vaccinations

All HIV-positive persons should receive vaccinations for pneumococcus.

- (Covalent) PCV13 first
- Eight weeks later, the (polysaccharide) PPSV23, influenza, and hepatitis B
- If CD4 >200/μL, varicella vaccine can be given

Monitoring the Immune System

CD4 monitoring and viral load testing can be compared to the staging of cancer in terms of assessing prognosis. They are indispensable for determining appropriate treatment.

CD4 cell count

The CD4 count is the most accurate method of identifying the infections or other diseases that the patient is at risk for, i.e., the risk of opportunistic infections.

- Provides an assessment of the extent of immunologic damage at the time of diagnosis
- Critical for deciding the timing of therapy
- Adequacy of response to antiretroviral medications
- Strongest predictor of disease progression and survival

Without treatment, CD4 count drops 50–100 cells per year.

The following is an approximate breakdown of when the risk of certain diseases begins to increase.

CD4 Count	Disease Risk
700–1,500/μL	Normal
200–500/μL	Oral thrush, Kaposi sarcoma, TB, Zoster
100–200/μL	*Pneumocystis carinii* pneumonia, disseminated histoplasmosis and coccidioidomycosis
<100/μL	Toxoplasmosis, *Cryptococcus*, cryptosporidiosis, disseminated herpes simplex
<50/μL	Cytomegalovirus; *Mycobacterium avium* complex; progressive, multifocal leukoencephalopathy (PML); CNS lymphoma

Note

While CD4 count is helpful for determining the adequacy of response to antiretrovirals, the best test for monitoring response to therapy is the HIV-RNA viral load.

Viral load monitoring

Tests now exist to give a numerical value to the quantity of HIV in the blood, "viral load." Monitoring of viral load is the best way to monitor response to antiretroviral treatment.

- High viral load indicates that CD4 level will drop more rapidly.
- High viral load indicates a greater risk of complications and a worse prognosis.
- With current assays, the goal is complete suppression of viremia with **<50–70 copies of HIV-RNA/mL**.

Note

Viral load monitoring in HIV can be compared to monitoring for glucose in diabetes.

Note

TB can be seen at any CD4 count.

Viral sensitivity/resistance monitoring

Viral sensitivity testing is done in the following situations:

- All patients prior to initiation of antiviral medications
- Patients who are not responding to current medications and require a change in treatment
- Pregnant women who are not fully suppressed on the initial combination of medications

Treatment failure first manifests with a rising PCR-RNA viral load.

Antiretroviral Therapy

First-line antiretroviral therapy is 2 nucleoside reverse transcriptase inhibitors (NRTIs) + an integrase inhibitor.

Preferred regimens include:

- Abacavir/lamivudinen/dolutegravir
- Tenofovir alafenamide/emtricitabine/dolutegravir
- Tenofovir alafenamide/emtricitabine/cobicistat/elvitegravir
- Tenofovir alafenamide/emtricitabine/raltegravir

NRTIs and integrase inhibitors inhibit the HIV replication cycle and terminate the DNA chain. NRTIs do so by blocking the action of the viral enzyme *reverse transcriptase*. Integrase inhibitors do so by blocking the action of the viral enzyme *integrase*.

- **NRTIs**
  - Zidovudine (also called azidothymidine): side effects include leukopenia, anemia, GI disturbance
  - Lamivudine (3TC): nothing additional to placebo
  - Emtricitabine: structurally related to lamivudine (rarely well-tolerated; side effects include lactic acidosis and severe hepatotoxicity)
  - Tenofovir, a nucleotide analog as compared to the others that are nucleo*side* analogs
  - Abacavir: side effects include hypersensitivity reaction in first 6 wks (rash, fever, nausea/vomiting, muscle aches), SOB (stop drug immediately and do not restart); recurrence of hyperactivity symptoms can be rapid and life-threatening

Note

- Because of greater long-term viral suppression, low resistance, and fewer side effects with current medications, **first-line antiretroviral therapy** is now 2 nucleoside reverse transcriptase inhibitors + an integrase inhibitor.
- Commonly used nucleoside reverse transcriptase inhibitors include **emtricitabine-tenofovir** and **abacavir-lamivudine**.

  - Tenofovir and emtricitabine (**both commonly used**)
  - Abacavir and lamivudine (**both commonly used**)
- **Integrase inhibitors**
  - Dolutegravir
  - Elvitegravir: give with cobicistat as a boost effect because it inhibits the P450 system (can elevate serum creatinine because it inhibits creatinine secretion)
  - Raltegravir

Second-line agents include:

- **Protease inhibitors (PIs)**: hyperlipidemia, hyperglycemia, and elevated liver enzymes; abnormal fat loss (lipoatrophy) from the face and extremities, with redistribution of fat in back of the neck and abdominal viscera; are potent inhibitors of CYP3A and have many drug-drug interactions
  - Indinavir: side effects include nephrolithiasis (4%) and hyperbilirubinemia (10%)
  - Ritonavir: side effects include severe GI disturbance
  - Darunavir
  - Lopinavir/ritonavir combination: side effects include diarrhea
  - Atazanavir: side effects include diarrhea and asymptomatic hyperbilirubinemia
- **Non-nucleoside reverse transcriptase inhibitors** (noncompetitive inhibitors of reverse transcriptase)
  - Efavirenz: side effects include neurologic; somnolence and confusion
  - Nevirapine: side effects include rash and hepatotoxicity

Guidelines for starting therapy are to **start therapy once HIV is diagnosed**, regardless of CD4 count. Viral sensitivity testing should be done in all patients prior to staring treatment.

- 2 nucleosides combined with an integrase inhibitor (**most common**)
- 2 nucleosides combined with a protease inhibitor or with efavirenz (**second-line**)

Emtricitabine, efavirenz, and tenofovir are available as a single pill once a day.

- Tenofovir can rarely cause Fanconi syndrome. Patients present with hypokalemia, hypophosphatemia, metabolic acidosis, and glycosuria. It can also cause demineralization.
- Tenofovir has 2 formulations: alafenamide (**preferred**, with fewer side effects) and disoproxil.

Giving **"boosted protease inhibitors"** is the practice of giving most protease inhibitors in combination with a low dose of ritonavir (also a PI). Ritonavir given alone as a PI has modest efficacy and significant drug interactions, but when given in a low dose with other PIs, it decreases their metabolism and enables higher drugs levels of the "boosted" PI over a prolonged period of time. This increases chances of success and also decreases pill burden.

- Any regimen that increases the CD4 count and drops the viral load to undetectable amounts (or close to) is considered adequate therapy.
- A drop of at least 50% of viral load in the first month is expected to indicate adequate therapy.

Note

Before giving abacavir, be sure to check HLA B5701. People carrying this allele are at risk for SJS.

Note

The **only statins safe with PIs** are rosuvastatin, pravastatin, and low-dose atorvastatin. Never give lovastatin or simvastatin in combination with a PI.

Pregnant, HIV-Positive Patients

Without treatment, approximately 25–30% of children born to HIV-positive mothers will truly be HIV positive. All children at birth will carry the maternal antibody to the virus and will be positive by ELISA testing, but only 25–30% will remain truly infected.

These patients should receive the following:

- Triple antiretroviral therapy (as nonpregnant people receive)
- Immediate therapy as soon as it is know that the patient is pregnant
- Intrapartum IV azidothymidine

Note

Most pregnant, HIV-positive women can have normal vaginal delivery.

The following medications are not recommended:

- Efavirienz
- Elvitegravir-cobicistat
- Tenofovir alafenamide
- Dolutegravir in first 8 weeks of pregnancy

C-section is required only when CD4 count and viral load are not controlled with medications (viral load >1000 copies/mL of HIV-RNA at time of delivery). Otherwise, do normal vaginal delivery. After delivery, the baby should receive zidovudine for 6 weeks.

Breast feeding is associated with transmission of the virus to the infant.

- If a pregnant woman is already on antiretrovirals, she should continue on them.
- If a pregnancy woman has high CD4 cells and does not need treatment for herself, combination therapy can end after delivery.

Postexposure Prophylaxis (e.g., Needlestick Injury)

All persons with serious exposure to blood containing body fluids of HIV-positive patients should receive emtricitabine-tenofovir and raltegravir.

Pre-Exposure Prophylaxis (PrEP)

Note

Do an HIV test on anyone with ITP, abrupt onset of severe and explosive psoriasis, severe and sudden seborrheic dermatitis, recurrent herpes zoster, or molluscum contagiosum.

People who are HIV-negative but have high risk behavior should be offered PrEP. On the exam, the question will make it clear that the HIV-negative person is high risk (unprotected sex with multiple partners, shares needles, or has an HIV-positive partner). The preferred agent is emtricitabine/tenofovir-disoproxil-fumarate, which will prevent transmission of HIV.

Patients should continue to take PrEP as long as they exhibit high risk behavior. This is more effect than using condoms (and on the exam, would be the correct answer over using condoms).

Acute HIV

Two weeks after being infected, the patient will present with fever, lymphadenopathy, sore throat, rash, myalgia/arthralgia, and headache (2–4 weeks after exposure).

- Rash: upper thorax, collar region, and face, scalp and extremities, including palms and soles
- Macules or maculopapules: small (5–10 mm), well-circumscribed, oval or round, pink to deeply red-colored
- Diagnosis is made with RT-PCR based viral load test or p24 antigen-testing

Immune reconstitution inflammatory syndrome (IRIS)

IRIS may be seen 3 days to months after starting ART in a patient with low CD4 counts. It can be seen with TB, *Mycobacterium avium* complex, Kaposi sarcoma, CMV, *Pneumocystis jiroveci* pneumonia (PJP), zoster, or *Cryptococcus neoformans*.

- Activation of an opportunistic infection as CD4 count increases
- Patient will have symptoms (e.g., shortness of breath and fever with PJP)
- Treat opportunistic infections; use steroids for severe symptoms
- Do not stop ART

TOXIC SHOCK SYNDROME

Toxic shock syndrome is seen with the use of tampons, sponges, and surgical wounds.

- *Staph aureus* (toxin TSST-1)
- Hypotension, fever, mucosal changes, desquamative rash on hands and feet.
- GI, renal, hepatic symptoms
- Treat with vancomycin and clindamycin

LEPTOSPIROSIS

Leptospirosis is a rare bacterial disease that is contracted by contact with the urine of rodents. It is caused by bacteria of the genus *Leptospira*.

- Renal and liver failure
- Myositis
- **Conjunctival** suffusion is pathognomonic
- Serology with ELISA
- Treat with penicillin, ceftriaxone, or doxycycline

TETANUS

Tetanus is a severe infectious complication of wounds caused by the toxin of *Clostridium tetani* (neurotoxin); takes 1–7 days to develop; spore forming, gram-positive rod.

Clinical Findings. Tonic spasms of voluntary muscles; respiratory arrest; difficulty in swallowing (dysphagia); restlessness; irritability; stiff neck, arms, and legs; headache; lockjaw; flexion of the arms and extension of the lower extremities; and high mortality rate. Diagnosis is clinical.

Treatment is prophylactic:

- Tetanus toxoid (Tdap) booster every 10 years
- Immediate surgical care, debride wound
- Antitoxin, tetanus immunoglobulin
- Penicillin 10–14 days

Wound Management		
Patient	**Not Tetanus Prone**	**Tetanus Prone**
	Linear, 1 cm deep cut, without devitalized tissue, without major contaminants, <6 hours old	Blunt/missile, burn, frostbite, 1 cm deep; devitalized tissue present + contaminants (e.g., dirt, saliva); any wound 6 hours old
Not completed primary or vaccination history unknown	Vaccine	Vaccine and TIG*
Completed primary series	Vaccine if >10 years since last booster	Vaccine if >5 years since last booster

*TIG = tetanus immunoglobulin (human)

Nephrology 8

Learning Objectives

- ❑ Describe the most commonly ordered renal diagnostic tests and their use
- ❑ Outline the approach to investigating kidney problems, fluid and electrolyte disorders, and acid-base disturbances
- ❑ Describe the presentation, diagnosis, and management of acute renal failure, renal tubular acidosis, glomerulonephritis, nephrolithiasis, hereditary cystic disease, and ESRD
- ❑ List the indication and complications of dialysis and criteria to qualify for renal transplantation
- ❑ Describe the causes of primary and secondary hypertension and their management

TESTS IN RENAL DISEASE

Renal diseases may be classified as glomerular, tubulointerstitial, or vascular. The kidney may also be affected by abnormalities in blood supply (CHF, renal artery stenosis) or drainage (ureteral stones, prostatic obstruction). When a patient develops renal disease, it usually presents as one of the following:

- Proteinuria, reflecting a damaged glomerular basement membrane
- Hematuria, reflecting inflammation
- Declining glomerular filtration rate (GFR)

Therefore, renal disease is best detected initially by urinalysis and serum creatinine.

Urinalysis

For the general population, there is no recommendation for routine urinalysis. For those with DM, however, secondary prevention of diabetic nephropathy is recommended; microalbumin/creatinine ratio on a spot urine specimen should be used and not urinalysis.

- **Protein.** The urine protein dipstick detects negatively charged proteins (e.g. albumin) but not other proteins such as immunoglobulin light chains. Proteinuria may be caused by glomerular or tubular disease, although glomerular disease leads to greater amounts. The lower limit of detection for protein on the UA is 300 mg/24 hours, too high to sensitively screen for early diabetic nephropathy. Detected proteinuria may reflect renal disease, but it may also be caused by fever, CHF, or severe exercise. Any positive urine dipstick for protein should be followed up by a quantitative study.
- **Heme and red blood cells** (RBC). The heme dipstick is positive when RBCs are present, but also when there is free hemoglobin (transfusion reactions) or myoglobin (rhabdomyolysis) in the urine. Red cells can be found in the urine from any cause of disease in the urologic system. Etiologies are stones, cancer, bleeding disorders, trauma to urinary system, and treatment such as cyclophosphamide (which causes hemorrhagic cystitis or glomerular disease). Hematuria is also from infections such as cystitis or prostatitis. The red cells change shape (dysmorphic) in some glomerular disease; other clues to glomerular disease are concurrent proteinuria and **RBC casts**, which are pathognomonic for glomerulonephritis.
- **Nitrites.** Gram-negative bacteria reduce nitrate to nitrite, which is a marker of urinary infection.
- **Glucose:** Glucosuria most often reflects hyperglycemia, but may also be caused by defective proximal tubular reabsorption, seen in Fanconi syndrome.
- **Bacteriuria.** By itself, the isolated finding of bacteria in the urine is of very limited significance. The most important exception is in pregnant women, since 30% of those with bacteriuria progress to pyelonephritis. Screen and treat as needed.
- **White blood cells** (WBC) may be due to pyelonephritis, cystitis, or intrarenal inflammation (e.g. eosinophils in eosinophilic granulomatosis). If eosinophils are suspected, they should be stained for with Hansel or Wright staining. If due to bacterial infection, the WBC should be accompanied by visible bacteria, but this may not be the case with all microorganisms (e.g., TB).
- **Renal tubular epithelial cells** appear in the urine during acute tubular necrosis, as dying tubular cells slough into the urine.
- **Casts** are collections of precipitated protein in the renal tubule, often capturing cells which are present there. The most significant casts are RBC casts (seen only in glomerulonephritis) and muddy brown granular casts (seen in acute tubular necrosis).

Table 8-1. Casts

Casts	Significance
Hyaline	Dehydration. These casts develop as an accumulation of the normal amount of tubular protein; they do not necessarily mean disease.
Red cell	Glomerulonephritis
Broad, waxy	Chronic renal failure
Granular	Also called "dirty" or "muddy"; are associated with acute tubular necrosis and represent accumulated epithelial cells
White cell	Pyelonephritis, interstitial nephritis

Urine Protein and Creatinine Concentration

Since the UA is an imperfect screen for small amounts of proteinuria, the best test for this is the spot urine collection for albumin and creatinine (has largely replaced the 24-hour collection done in the past). The ratio of albumin to creatinine is a good estimate of the albumin that would have been collected in a 24-hour collection, and is much easier to do. A 30–300 mcg albumin/mg creatinine suggests incipient diabetic nephropathy in at-risk patients, and would prompt starting an angiotensin-converting enzyme (ACE) inhibitor.

Serum Creatinine, BUN, and Estimated GFR

The glomerular filtration rate (GFR) falls early in many renal diseases, without symptoms. Sensitive testing is thus needed to detect early chronic and acute renal injury. Creatinine, a metabolic product of skeletal muscle, is the main measure of GFR.

An isolated serum creatinine (SCr) test may be deceiving, since it may be low (0.5 mg/dL) just because of decreased muscle mass or high (1.6 mg/dL) due to large muscle bulk. More muscle means more creatinine. Therefore, **serum creatinine values should always be compared to a given patient's baseline**. A doubling of the SCr means a 50% reduction in their GFR.

- Creatinine needs some time to rise. Even if the patient becomes anuric, creatinine will rise only at a rate of 0.5–1.0 point per day. This rise will be faster if the body muscle mass is greater.
- Hence, if the creatinine goes from 1 to 3 over a period of 2 days in a patient with renal injury, this is consistent with nonfunctioning kidneys.

Given the limitations of the isolated serum creatinine, options for better estimation of the GFR include the **creatinine clearance**, which requires a 24 hour urine collection, and the **estimated GFR (eGFR)**, which requires no urine and may be calculated from the patient's SCr, age, race, height, weight, and sex. This builds an estimate of muscle mass to correct the final number. **The eGFR is now the most commonly used way to determine a patient's renal function**. It is not useful if the patient's SCr is not at baseline (decreasing or increasing) and should only be used at steady state. The same limitation applies to the creatinine clearance.

Serum BUN is less useful than the creatinine for determining renal function. While it does increase in acute or chronic kidney injury, it may also be falsely elevated even when renal function is normal, in response to increased protein load in the diet or GI bleed. The BUN is derived from protein waste products; blood in the gut acts like a big protein meal and is catabolized to urea. The BUN can be falsely low when there is liver disease, malnutrition, or SIADH.

The BUN is most useful when compared to the serum creatinine, since a ratio >20:1 may suggest prerenal azotemia.

Renal Sonography (Ultrasound)

Renal sonography is the most common test used in renal visualization. It has several uses:

- Detects hydronephrosis in renal obstruction, allowing prompt decompression
- Shows small or scarred kidneys in advanced chronic kidney disease, allowing differentiation from the normal appearing kidneys seen in acute kidney injury
- Shows renal cysts and tumors
- Detects kidney stones in the renal pelvises

ACUTE KIDNEY INJURY

Acute kidney injury (AKI), previously called *acute renal failure*, is a rapid decline in the glomerular filtration rate (elevated BUN and creatinine) over several hours to days. There is no precise duration to define it as *acute*. For example, in rhabdomyolysis or contrast-induced renal failure, it may develop over several hours, while in aminoglycoside toxicity it may take 1–2 weeks.

AKI must be distinguished from **chronic kidney disease** (CKD), which is the slow decline in GFR over years (seen in many glomerular diseases such as diabetic nephropathy).

The distinction between AKI and CKD cannot be made with a single serum creatinine test; it requires serial determinations. The renal sonogram (U/S) can also help in the distinction:

- AKI often shows normal kidneys, despite declining function.
- CKD often shows small or scarred kidneys.

Progressive kidney disease may life-threatening. Clinical presentation includes:

- Hyperkalemia, severe acidosis, and fluid overload/pulmonary edema
- Anemia, bone disease, and pericarditis
- Bleeding diathesis due to platelet dysfunction
- Altered mental status

AKI is **classified** as prerenal, postrenal, or intrarenal based on the site and mechanism of injury.

- **Prerenal AKI** means decreased perfusion of the kidney (e.g., CHF, renal artery stenosis, volume depletion). The kidney itself is healthy.
- **Postrenal AKI** indicates renal obstruction, causing decreased drainage from the kidney and decreased forward flow of urine (e.g., stones, prostatism, pelvic malignancy). The kidney itself is healthy.
- **Intrarenal AKI** means a reduction in GFR due to a renal tubular, interstitial or glomerular disease (e.g. glomerulonephritis, acute tubular necrosis, acute interstitial nephritis). The kidney is defective.

Clinical presentation. Most AKI is asymptomatic at first, since uremic symptoms do not typically occur until >75% of GFR has been lost. It is commonly a hospital diagnosis, as AKI often accompanies severe illness. Clinical hints of early AKI might include:

- Decreased urine output
- Hypotension or orthostasis (prerenal)
- Hypertension (intrarenal)
- Edema (intrarenal)

Serial measurements of the serum creatinine concentration (SCr) should show rising levels each day. Once a stable value of the SCr is reached, the estimated GFR eGFR can be calculated using standard formulas.

- Urinalysis and fractional excretion of sodium are used to evaluate causes of intrarenal AKI.
- Renal U/S is used to rule out postrenal AKI.
- Serum Na, K, and HCO3, hematocrit/hemoglobin should be monitored.

Note

- **Renal insufficiency** or **azotemia** is AKI but does not require dialysis. (*Azotemia* literally means the buildup of azole groups or nitrogen in the blood.)
- **Uremia** (or ESRD) is very severe AKI or CKD that requires dialysis or transplantation to save life.

Note

Uremia does not necessarily imply CKD. Although most patients develop uremia after years of CKD, it is possible to become uremic in as little as 1–2 weeks with a severe illness causing AKI (e.g., rhabdomyolysis).

Because they are more easily reversed, prerenal and postrenal AKI should always be excluded before launching a workup of renal disease when a declining GFR is detected.

Prerenal Acute Kidney Injury

Prerenal azotemia is a form of AKI caused by diminished perfusion of the kidney. The kidney itself is normal. If the kidney could receive adequate perfusion, the BUN and creatinine would normalize. The causes of prerenal azotemia include:

- Hypovolemia: dehydration, burns, poor oral intake, diuretic, vomiting, diarrhea, sweating, hemorrhage, hypocortisolism, hypoaldosteronism
- Hypotension: septic shock, cardiogenic shock, anaphylactic shock, hepatorenal syndrome
- Third spacing of fluids: peritonitis, osmotic diuresis, low oncotic pressure (hypoalbuminemia of cirrhosis, nephrotic syndrome)
- Decreased renal blood flow: CHF, constrictive pericarditis, renal artery stenosis, aortic coarctation
- Renal arteriolar vasoconstriction/vasodilation: hypercalcemia, cyclosporine, tacrolimus, NSAIDs, ACE inhibitors

Diagnosis is usually made by clinical exam. Volume-depleted patients present with signs of orthostatic or frank hypotension and tachycardia. Skin turgor may be reduced, reflecting low extracellular volume.

In contrast, the prerenal AKI seen in severe CHF, constrictive pericarditis, or coarctation may show edema and fluid overload, yet the kidney is receiving no/low perfusion, thus the rising BUN and creatinine. This demonstrates a reduction of effective arterial volume a physiologic term for perfusion of organs, determined by intravascular volume, blood pressure, and cardiac output.

Regardless of the cause of prerenal AKI, patients may show:

- Elevated serum creatinine concentration
- Normal urinalysis
- Serum BUN:creatinine ratio >20:1 (normally 10:1 in other types of AKI); the BUN elevates because urea undergoes increased proximal tubule reabsorption in states of high sodium absorption (e.g., volume depletion)
- Low urine sodium concentration (<10 mEq/L)
- Low fractional excretion of sodium (FeNa <1%) because the kidney perceives the body as being volume-depleted, leading to a vigorous sodium and water reabsorption by the kidney
- High urine osmolality (>500 mosm/kg) and specific gravity (>1.010)

The urine tests reflect the high renal sodium and water reabsorption driven by the low renal perfusion.

Renal artery stenosis, especially if bilateral, may result in prerenal AKI with a rising creatinine. The kidneys themselves are normal. Similar to the case of renal obstruction, bilateral disease is required for detectable AKI, since loss of a single kidney may be compensated by recruitment of reserve nephrons in the remaining kidney, maintaining the GFR near normal.

In renal artery stenosis, although systemic BP may be markedly elevated (due to high renin/AT/aldosterone levels), the low renal blood flow still leads to AKI. Here, the elevated systemic BP does not matter; all that matters is how much blood is getting to the kidney. This effect is amplified with the use of ACE inhibitors, which will additionally diminish renal perfusion in this setting. Treatment is angioplasty/stenting.

Hepatorenal syndrome is AKI based entirely on the presence of hepatic failure. The kidneys are themselves normal. The rise in BUN and creatinine is believed to be due to an intense vasoconstriction of the afferent arteriole in response to systemic vasodilation caused by the hepatic failure. The local renal vasoconstriction causes decreased renal perfusion and AKI. The syndrome does not respond to volume expansion, unlike AKI in hepatic failure due to simple ECV volume depletion. Lab evaluation is similar to other causes of prerenal AKI. Intrinsic renal disease should be excluded to make a diagnosis (e.g. patients should have a normal urinalysis). A key diagnostic step is lack of improvement of the SCr after a bolus infusion of colloid fluid (e.g. albumin). Treatment is correction of the underlying liver disease (e.g. liver transplantation). Since the underlying physiology is systemic vasodilation, treatment with vasoconstrictors may be useful. Midodrine, an alpha agonist, and octreotide may be beneficial.

- ACE inhibitors may cause prerenal AKI, especially in patients with volume depletion, bilateral renal artery stenosis, or other causes of prerenal AKI. The renal failure is caused by vasodilation of the efferent arteriole.
  - Angiotensin-II constricts the efferent arteriole, a mechanism used to maintain glomerular perfusion pressure in the face of low blood flow. ACE inhibitors block this adaptation, causing a transient decrease in GFR.
  - Despite this ability of ACE inhibitors to worsen GFR, their overall effect on the kidney is to diminish proteinuria and the rate of progression to uremia and renal failure.
  - This beneficial effect is most likely secondary to the decrease in intraglomerular hypertension.
  - ACE inhibitors decrease proteinuria by 35–45% (particularly in patients with diabetic nephropathy).
- NSAIDs may cause prerenal AKI, especially in patients with volume depletion, bilateral renal artery stenosis, or other causes of prerenal AKI. The renal failure is caused by vasoconstriction of the afferent arteriole.
  - NSAIDs inhibit the action of the vasodilatory prostaglandins that maintain dilation of the afferent arteriole (important in maintaining GFR in the face of volume depletion).
  - A similar effect is seen in the calcineurin inhibiting transplant drugs cyclosporine and tacrolimus, which both vasoconstrict the renal arterioles, causing reversible prerenal AKI.
  - NSAIDs may also affect the kidney by causing intrarenal AKI, specifically acute interstitial nephritis, papillary necrosis, or secondary forms of membranous glomerulopathy and minimal change disease.

Postrenal Acute Kidney Injury

Postrenal azotemia is caused by any decrease in the outflow of urine. This may come by obstruction of any part of the renal collection system (renal pelvises to urethra). In order to cause AKI the obstruction must be **bilateral**, since obstruction of a single kidney can be compensated for by the remaining kidney's recruitment of reserve nephrons, maintaining a normal GFR. (This is also why donating a single kidney for transplantation does not change your serum creatinine.) Common causes of postrenal AKI include:

- Renal pelvises: bilateral stones
- Ureters: bilateral stones, bilateral ureteral disease e.g., retroperitoneal fibrosis, strictures
- Bladder: stones, clots, cancer obstructing bilateral ureteral outflow
- Prostate: hyperplasia and cancer
- Neurologic disease: Neurogenic bladder: patients have a history of obstructive symptoms followed by sudden onset of oliguria or anuria. This may be due to multiple sclerosis, spinal cord lesions, or peripheral neuropathy.

Clinical Presentation: Patients may experience a distended bladder in prostatism or neurologic disorders. Urine output may diminish or cease, proceeded by incomplete voiding in prostate or bladder diseases. Patients may have pain over the bladder (prostatism) or flanks (stones).

Diagnosis: The serum creatinine elevates unless the disease is unilateral.

- BUN and creatinine will initially elevate in a ratio 20:1 as it does with prerenal azotemia.
- Later the BUN:creatinine ratio will lower to 10:1.

The urinalysis is variable, from normal (neurogenic bladder) to hematuria (stones, bladder cancer, clots).

Diagnosis is confirmed by seeing bilateral hydronephrosis on renal sonogram or non-contrast CT scan. This should be done early in all patients with AKI, since prompt relief of obstruction is essential.

Prostate or bladder outflow disease may be detected by finding large volumes of urine in the bladder after passing a Foley urinary catheter (a large post-void residual volume). After urinating (voiding), there should be no more than 50 mL of urine left in the bladder. If this post-void residual is markedly elevated, it implies an obstruction to the flow of urine out of the bladder.

Treatment is based on quickly relieving the cause of the obstruction: For bladder/prostate disease, do Foley catheter insertion. For ureteral/pelvic obstruction, do nephrostomy tube insertion (percutaneous or transurethral).

Clinical Recall

Which of the following lab values is most likely in patients with prerenal azotemia?

A. BUN:Cr >20:1, Urine Na <20, FENa <1%, Urine Osmolality >500

B. BUN:Cr 10:1, Urine Na >40, FENa >1%, Urine Osmolality <350

C. BUN:Cr >20:1, Urine Na >40, FENa >4%, Urine Osmolality <350

D. BUN:Cr <10:1, Urine Na >40, FENa >1%, Urine Osmolality <500

E. BUN:Cr >20:1, Urine Na <20, FENa >4%, Urine Osmolality <350

Answer: A

Intrarenal Acute Kidney Injury

AKI due to intrarenal disease may result from:

- Tubular disorders: acute tubular necrosis, crystal-formations with intrarenal obstruction
- Interstitial disorders: acute and allergic interstitial nephritis
- Acute microvascular disorders: cholesterol embolization and papillary necrosis

Glomerular disease more often causes CKD, except for rapidly progressive glomerulonephritis, where renal failure may be more abrupt (see Glomerular Disease section).

Tubular disorders

Acute tubular necrosis (ATN) is acute renal failure on the basis of tubular damage and necrosis, leading to reduced solute clearance, AKI, and diminished electrolyte and water regulation. Causes include ischemia and hypoperfusion of the kidney (shock, sepsis, heart failure) and tubular toxins (aminoglycosides, contrast dyes, amphotericin, myoglobin [rhabdomyolysis], cisplatin).

Ischemic and toxic effects may be additive, increasing the risk of ATN. The degree, and especially the duration, of ischemia or toxic exposure are important to the prognosis and recovery from ATN. The longer the duration of hypotension/hypoperfusion, the greater the chance of ATN.

With ATN there is often an initial phase that appears similar to prerenal AKI, as the kidney is hypo-perfused. Next comes a reduction/cessation of urine flow (oligo- or anuria) as the tubules necrose and the glomerular ultrafiltrate back-leaks into the blood instead of forming urine. Finally, the tubules regenerate and a polyuric phase may occur. Not all patients go through each stage; for instance, some AKI is non-oliguric (e.g., aminoglycosides).

Diagnosis. With ischemic ATN, the BUN and creatinine will initially rise in a 20:1 ratio similar to prerenal AKI. This reduces to 10:1 as ATN tubular injury becomes established.

With severe or prolonged injury, the tubular cells will necrose and slough off into the urine and become visible as renal tubular epithelial cells or granular/muddy brown/pigmented casts. The rising serum creatinine (over days) is accompanied by reduced urine output or anuria. If available, urine findings can help to distinguish ATN from prerenal AKI.

Table 8-2. Confirming Prerenal versus ATN Based on Lab Values

	Prerenal AKI	ATN
Urine osmolarity	>500	<350
Urine Na+	<20	>40
FeNa+	<1%	>1%
Urine sediment	Scant	Full (brownish pigmented granular casts, epithelial casts may be seen)

Infusion of normal saline is also used to distinguish ATN from prerenal AKI, as only the latter will respond with a decreased SCr.

Treatment is correction of the underlying cause. No treatment can reverse renal failure. Monitor volume status and serum electrolytes.

- Volume repletion with normal saline to ensure there is no prerenal component and to reduce (but not reverse) contrast-induced renal failure
- Diuretics only for critical pulmonary edema; do not "convert" oliguric ATN to the non-oliguric type
- Dialysis if uremic symptoms occur (stop once tubules recover)
- ATN may be caused by filtered pigment injury to the tubules from myoglobin (in rhabdomyolysis) or hemoglobin (in hemolytic anemia).
- Rhabdomyolysis can be caused by sudden/severe crush injury, seizures, severe exertion, or by hypokalemia, hypophosphatemia, or medications (e.g., statins). Large amounts of released myoglobin are filtered into the nephron and cause tubular toxicity and ATN. Similarly, in massive hemoglobinuria from ABO incompatibility filtered hemoglobin causes tubular toxicity. The toxicity is because the pigment is directly toxic to the tubular cells, as well as from precipitation of the pigment in the tubules. The degree of toxicity is related to the duration of contact of the tubular cells with the hemoglobin or myoglobin, so is compounded by dehydration.

Diagnosis: Rhabdomyolysis with myoglobinuria is confirmed with the following:

- Markedly elevated serum CPK level (a biochemical marker of skeletal muscle neurosis); for nephrotoxicity to occur, level must be in 10,000–100,000 range (normal ≤500)
- Urinalysis dipstick positive for blood but with no red cells visible. This is because myoglobin can react with the heme reagent on the dipstick. Free hemoglobin will do the same thing.
- Rapidly rising serum creatinine level due to ATN
- Hyperkalemia: check the ECG for peaked T waves
- Metabolic acidosis with decreased serum bicarbonate
- Hyperphosphatemia secondary to muscle breakdown
- Hypocalcemia secondary to the deposition of calcium in damaged muscles and complexing with high phosphate.
- Hyperuricemia due to release of purines from damaged muscles

Treatment is normal saline to increase urine output and decrease toxin contact time. If there is little response, add mannitol, an osmotic diuretic. Alkalinizing the urine with bicarbonate may or may not be useful.

ATN Due to Drugs. The most common toxins that cause ATN are aminoglycosides, IV contrast agents, amphotericin, and cisplatin. For patients on multiple drugs, differentiation of ATN from acute interstitial nephritis is often difficult:

- Allergic interstitial nephritis occurs with the first dose, and is associated with fever, rash, joint pain, and eosinophils in both blood and urine. ATN lacks these.
- Drugs causing ATN often take days to weeks to produce enough cumulative toxicity to cause renal failure. Symptoms are those of acute kidney injury.

The clinical and lab evaluation is as described in the ATN section. There is no test which can confirm a specific toxin as the etiology of the renal failure. Other causes of renal failure must first be excluded, and the toxin must be identified and promptly withdrawn. There is no specific therapy that can reverse the renal insufficiency of any direct-acting toxin.

- **Aminoglycosides**. Aminoglycoside-related nephrotoxicity (10–20% of all drug-induced nephrotoxicity) is usually reversible. Unlike contrast dyes, aminoglycoside toxicity **takes 5–10 days of administration** to result in toxicity. The likelihood of toxicity is associated with high trough levels.
  - Tobramycin is less nephrotoxic than gentamicin or amikacin.
  - Renal failure due to aminoglycosides is often non-oliguric (so K^+ is not usually elevated).
  - Hypokalemia and hypomagnesemia predispose the patient to aminoglycoside toxicity.
  - To prevent, limit duration of use and reduce trough levels by giving the antibiotic once a day. Dosing 1×/day allows high bactericidal levels with the same efficacy and very low trough levels.
- **Amphotericin B.** This antifungal agent is associated with renal insufficiency as well as distal renal tubular acidosis (non-anion gap metabolic acidosis with hypokalemia and high urine pH). Like aminoglycosides, it occurs only **after several days or weeks** of amphotericin use, and is usually reversible with prompt discontinuation of the drug.
- **Contrast Agents.** Unlike the antibiotics, radiocontrast used in radiology can result in renal failure **in as little as 12–24 hours after the use of the agent**. The rise in creatinine peaks at 3–5 days after the injury. Initial vasoconstriction may be reflected in a "prerenal" lab picture, i.e. BUN: Cr of >20:1 and low urine Na. Underlying renal disease, DM, and advanced age increase the risk for ATN. Prevention is with **normal saline** infusion before the agent is administered. N-acetyl cysteine and sodium bicarbonate are often added but are of uncertain value.
- **Other Drugs.** Cisplatin accumulates in tubular cells and causes ATN in 20-30% of patients. Pentamidine, used for pneumonia in AIDS patients, is associated with ATN in 20–30% of patients.

Precipitation of crystals within the tubules can reduce urine flow and GFR, and may occur via endogenous or exogenous (ingested) substances and drugs.

- **Uric acid** toxicity occurs via intratubular crystallization and usually occurs in the setting of **tumor lysis syndrome** after treatment of leukemias and lymphomas. Patients show AKI, oliguria, severe hyperuricemia, hyperkalemia, and metabolic acidosis. Prevention is with vigorous hydration, sodium bicarbonate, and allopurinol prior to receiving chemotherapy. Allopurinol reduces the production of uric acid by inhibiting conversion of xanthine to hypoxanthine to uric acid. Uric acid stones precipitate in an acidic urine, unlike oxalate crystals, which precipitate in alkaline urine. Separately, gout may cause CKD through a slower and milder version of intrarenal urate deposition.
- **Oxalate crystals** cause AKI following **ethylene glycol overdose** after ingestion of antifreeze. Patients display intoxication, an anion gap metabolic acidosis and AKI. Diagnosis is confirmed with oxalate crystals seen on urinalysis (oxalate crystals are shaped like envelopes). Treatment is normal saline, sodium bicarbonate, and **fomepizole** to prevent the conversion of ethylene glycol to toxic oxalic acid. Separately, chronic hyperoxaluria and oxalate kidney stones can be caused by Crohn disease because of fat and calcium malabsorption.
- **Immunoglobulins and light chains** cause AKI in multiple myeloma, where renal filtration of light chains may lead to their precipitation in the tubules and to direct tubular toxicity. Both lead to AKI. The urinalysis may be normal, since the dipstick does not detect the positively charged light chains. Diagnosis is with urine protein electrophoresis. Separately, the light chains may cause proximal tubular dysfunction (Fanconi syndrome with glucosuria, aminoaciduria, phosphaturia, proximal RTA) or AA amyloidosis with glomerular damage.
- **Drugs** may precipitate in the tubule to cause AKI. Indinavir is a protease inhibitor that results in AKI due to the drug precipitating in the tubules. Indinavir stones may be seen on a spiral CT scan.

Interstitial disorders

Acute interstitial nephritis (AIN) accounts for 10–15% of intrinsic AKI. Histopathology shows a robust interstitial inflammation with eosinophils. This allergic reaction can take the form of a rash, Stevens-Johnson syndrome, hemolysis, and/or AIN.

- Cause is usually an adverse immunologic effect to medication that commonly cause allergies, i.e., penicillin, cephalosporins, sulfa drugs, allopurinol, rifampin, and quinolones.
- NSAIDs also cause a form of AIN lacking the eosinophiluria and the severe allergic symptoms (i.e., lacking rash, fever or joint pain, but presenting with a usually asymptomatic rise in serum creatinine).
- AIN is less commonly caused by infections themselves; specifically, leptospirosis, legionella, CMV, rickettsia, and streptococci.
- Rarely, AIN is caused by an autoimmune disorder such as SLE, Sjögren syndrome, sarcoidosis, and cryoglobulinemia. These are more likely to harm the kidney via glomerulonephritis.

Fever is seen in most patients with AIN. It can be very difficult to determine if the fever is from the underlying illness or from the AIN. Rash is present in 25–50% of patients. Joint pain is common because AIN acts somewhat like serum sickness.

Note

Other medications causing AIN include NSAIDs, allopurinol, and proton pump inhibitors.

Note

Any sulfa drug can cause an allergic reaction. Besides antibiotics, other examples of sulfa drugs are diuretics such as thiazides, furosemide, and acetazolamide.

Lab studies: The best initial test for AIN is a urinalysis (UA) looking for **white cells**, then **staining for urine eosinophils** (Hansel or Wright stain of the urine). While the kidney biopsy is most accurate, it is rarely done, since patients resolve following discontinuation of the antibiotic. Biopsy is used only in uncertain cases. NSAID-induced AIN typically lacks eosinophiluria and eosinophilia.

Other abnormalities may include eosinophilia, hematuria/mild proteinuria, and increased serum IgE levels.

Treatment. AIN should resolve spontaneously after stopping the offending agent; there is no specific therapy. If renal failure persists or worsens, consider a short course of steroids.

Acute microvascular disorders

Atheroembolic disease (cholesterol emboli syndrome). AKI may develop in some patients with severe atherosclerosis following an invasive arterial procedure (e.g., an arteriogram). Cholesterol emboli scatter throughout the body, including to the kidney. Look for a patient who undergoes a vascular catheter procedure such as angioplasty, who develops bluish discoloration of the fingers and toes, livedo reticularis, and AKI several days later. Labs show **AKI with eosinophilia, low complement levels**. Although the most accurate test is a skin biopsy to see cholesterol crystals in the skin, this is rarely done. There is no therapy for atheroembolic disease.

Acute papillary necrosis is AKI associated with occlusion of small renal capillaries, leading to the ischemia and sloughing of renal papillae, the medullary segments involved in urine concentration, and the least oxygenated area of the kidney. It is the nephron segment most vulnerable to hypoxia or sluggish blood flow. Papillary necrosis is seen in patients with a history of sickle cell disease, diabetes, urinary obstruction, chronic pyelonephritis, or chronic analgesic use, esp. NSAIDs. Volume depletion concentrates the blood and increases the risk. Look for the sudden onset of **flank pain, hematuria, pyuria, and fever** in an at-risk patient, esp. those in sickle crisis. This can be very similar to acute pyelonephritis. Like pyelonephritis, the urinalysis will show white and red cells. Unlike pyelonephritis, there will be no bacteria, and no organisms grow on culture. The patient may sometimes note red "chunks" in the urine that may cause confusion with kidney stones, but the referred ureteral pain of stones is absent.

The most accurate diagnostic test for papillary necrosis is **CT scan**, which will show "bumpy" contours in the renal pelvis where the papillae have sloughed off. There is no specific therapy for papillary necrosis.

GLOMERULAR DISEASES

Glomerular diseases are the most common cause of chronic kidney disease and dialysis-requiring renal failure. The most common of these in the developed world is diabetic nephropathy.

Most glomerular diseases are also called **glomerulonephritis** (GN) or inflammation of the glomerulus, often as the result of an autoimmune event, circulating antibodies, or vasculitis. A few are non-inflammatory and caused by other mechanisms such as hypertensive nephrosclerosis (prolonged high BP), Alport syndrome (defective Type IV collagen in the glomerular basement membrane), and hemolytic-uremic syndrome (microthrombi in renal small vessels).

GN may be classified as follows:

- Primary disease without systemic illness (e.g., membranous GN, IgA nephropathy)
- Secondary disease due to systemic illness (e.g., post-infectious GN, diabetic nephropathy, lupus nephritis)

Based on presentation, it may be further classified as follows:

- Nephritic (sometimes called "acute GN") with hematuria, RBC casts, edema, hypertension, and renal failure (e.g., post-infectious GN, Goodpasture syndrome)
- Nephrotic with heavy proteinuria, hyperlipidemia, edema, and hypertension (e.g., minimal change disease, diabetic nephropathy)
- Rapidly progressive GN: hematuria, usually nephritic, accompanied by sub-acute renal failure (over 1-2 weeks), often with crescents seen on biopsy

Many glomerular diseases can be diagnosed using clinical evaluation and specific serologies, but the definitive diagnosis is usually made by **renal biopsy**, especially when there is heavy proteinuria or renal insufficiency. In these cases biopsy is usually needed, since treatment varies depending on histology.

Table 8-3. Common Glomerular Diseases

Nephritic Diseases	Nephrotic Diseases
Primary	**Primary**
IgA nephropathy	Membranous GN
Idiopathic rapidly progressive GN	Focal segmental glomerulosclerosis (FSGS)
	Membranoproliferative GN (also nephritic)
Secondary	Minimal change disease
Postinfectious GN	
Goodpasture syndrome	**Secondary**
Granulomatosis with polyangiitis	Diabetic nephropathy
Eosinophilic granulomatosis with polyangiitis	Amyloidosis
IgA nephropathy (Berger disease)	Lupus nephritis (also nephritic)
Lupus nephritis (also nephrotic)	
Cryoglobulinemia	
Membranoproliferative GN (due to hepatitis C)	
Polyarteritis nodosa	
Other Glomerular Diseases (usually neither nephritic nor nephrotic)	
Hemolytic-uremic syndrome/TTP	Alport Syndrome
Hypertensive nephrosclerosis	

Nephritic Diseases

Nephritic GN is characterized by hematuria, edema, red cell casts, and hypertension. The red cells often develop an abnormal shape (called "dysmorphic"), which distinguishes them from non-glomerular hematuria due to stones, bladder cancer, or infection. Small or moderate proteinuria is also common.

- The edema of glomerular disease may be anywhere in the body, but is usually first seen in dependent areas (ankles). It is caused by avid renal sodium retention, so labs show a low urine sodium, with fractional excretion of sodium <1%.
- With the salt and water retention, hypertension also develops.
- Nephritic diseases show modest amounts of protein in the urine, with a daily total <2 grams per 24 hrs. In contrast, nephrotic syndrome does not begin until >3.5 grams per 24 hrs.
- The most important distinction between nephritic and nephrotic syndrome is the hematuria (in nephritic) and degree of proteinuria (>3.5 gm/24 hrs in nephrotic).

A good physical exam is crucial, since half are associated with other systemic vasculitides.

In nephritic diseases **the single most important test for diagnosing GN is usually the renal biopsy**. Exceptions are post-infectious GN, where no biopsy is usually done, and systemic vasculitis, where skin or lung biopsy is easier and less risky. Biopsy is always done if the patient is developing subacute renal failure (rapidly progressive GN).

Table 8-4. Causes of Nephritic Syndrome

Vascular (Systemic) Disease	Glomerular Disease
Granulomatosis with polyangiitis	Postinfectious GN
Eosinophilic granulomatosis with polyangiitis	Goodpasture syndrome
Henoch-Schönlein purpura (renal lesion = IgAN)	IgA nephropathy (IgAN)
Polyarteritis nodosa	Lupus nephritis (SLE) (can also be nephrotic)
Cryoglobulinemia	Idiopathic rapidly progressive GN
	Membranoproliferative GN (can also be nephrotic)

Nephritic vascular diseases

The following disorders show a nephritic clinical presentation but also involve diffuse vascular injury.

Granulomatosis with polyangiitis (Wegener granulomatosis) is characterized by systemic vasculitis that most often involves the kidney, lung, and upper respiratory tract such as the sinuses or middle ear. It can also involve the skin (50%), eyes (50%), joints, and GI tract.

Note

All forms of vasculitis are characterized by fever, weight loss, and a generalized malaise.

Neuropathy may be a symptom. If a patient with chronic upper and lower respiratory illness does not respond to antibiotics and then develops renal failure or hematuria, consider this disorder.

- Other lab abnormalities include elevated ESR, rheumatoid factor (50%), anemia, and leukocytosis. These findings are nonspecific.
- Best initial test is C-ANCA or antiproteinase-3 antibody.
- Most accurate test is biopsy of the kidney, nasal septum, or lung, looking for granulomas (sinus biopsy, specifically the nasal septum, is less sensitive and has more false-negatives).
- P-ANCA or anti-myeloperoxidase antibody is found at much lower frequency.
- Complement levels are normal.
- Treatment: cyclophosphamide and glucocorticoids

Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) is a vasculitis similar to granulomatosis with polyangiitis, characterized by chronic lung involvement, neuropathy, skin lesions, GI, cardiac, and renal involvement.

- Diagnostic clues include a history of asthma, eosinophilia, or another atopic disease and elevated eosinophils.
- P-ANCA often positive but is nonspecific.
- Most accurate test is lung biopsy showing the granulomas and eosinophils.
- Treatment: cyclophosphamide and glucocorticoids

PAN is a systemic vasculitis of small- and medium-sized arteries that affects virtually every organ in the body *except the lung*. Renal involvement is common and manifests as hypertension, renal insufficiency, and hemorrhage due to microaneurysms. Like all vasculitis, PAN is associated with fever, weight loss, and malaise. Other organs involved include the skin, eyes, muscles, GI tract, heart, kidneys, and neurologic system. Abdominal pain and joint pain may be prominent. The abdominal pain may mimic mesenteric ischemia, and the pain will occur with eating. Anemia and an elevated sedimentation rate are present but are too nonspecific to be useful.

- Diagnostic clues include multiorgan vasculitis, sparing the lungs.
- Most accurate test is biopsy of an affected area.
  - If there are neurologic symptoms, sural nerve biopsy is high-yield.
  - If there is abdominal pain, angiogram of the involved vessels in the GI tract may eliminate the need for a biopsy.
- Hepatitis B (10–30% of patients, especially injection drug users)
- P-ANCA (uncommon)
- Treatment: cyclophosphamide and glucocorticoids

Renal disease from **cryoglobulinemia** shows the lesion of membranoproliferative GN (type 1) and is associated with chronic hepatitis C, and less commonly hepatitis B.

- Diagnostic clues include hepatitis C and positive serum cryoglobulins.
- Presentation may be nephritic and/or nephrotic.
- Associated with joint pain, neuropathy, and purpuric skin lesions
- No GI involvement
- Elevated ESR and low levels of complement
- Treatment: treat the underlying chronic hepatitis; for severe disease (renal failure, heavy proteinuria), pulse doses of steroids and plasmapheresis

Note

Wegener granulomatosis is now called granulomatosis with polyangiitis (Wegener). Churg-Strauss syndrome is now called eosinophilic granulomatosis with polyangiitis.

Note

Heavy proteinuria and RBC cases are uncommon in PAN, as it is not a true glomerulonephritis (even though there is hematuria).

Nephritic glomerular diseases

The following disorders show a nephritic clinical presentation, but the disease process is limited to the glomerulus.

Postinfectious GN is the classic nephritic disease, with dark urine, hypertension, and edema developing suddenly **1–2 weeks after strep pharyngitis**. If not caused by group A beta hemolytic streptococci (*Streptococcus pyogenes*), it may be caused by throat or skin infection with *Streptococcus pyogenes* (although rheumatic fever occurs only with the strains that cause pharyngitis). Poststreptococcal GN occurs in 10–15% of patients with pharyngitis infected with a nephritogenic strain.

Virtually any infectious agent can cause postinfectious GN, including hepatitis B and C, CMV, and chronic staphylococcal infections such as endocarditis. In the pre-antibiotic era, GN was the most common cause of death from endocarditis. The disease is usually self-limited, so it is unusual among the GNs in not requiring a biopsy if there is a characteristic history and positive serology.

The key to diagnosis is an association with infection. The best initial test is the **antistreptolysin (ASO)** or **antihyaluronic acid (AHT)**.

- Complement levels, particularly C3, are low.
- Renal biopsy is rarely needed, but if done would show epithelial "humps" on electron microscopy. IgG and C3 will be deposited in the mesangium.

Treatment is supportive (management of fluid overload and hypertension with diuretics). Most cases resolve spontaneously. Antibiotics will eradicate the organism from the pharynx. Glucocorticoids are sometimes used for unusual persistence of proteinuria or renal failure in adults.

Goodpasture syndrome (GPS) is an idiopathic **renal and lung disease** characterized by a unique anti-glomerular basement membrane antibody. Presentation includes **hematuria and hemoptysis**. Aside from the lungs and kidneys, GPS does not affect other sites in the body, thus an **absence of skin or eye findings** is a clue to the diagnosis. When there is lung involvement (65%), patients present with hemoptysis, cough, and/or shortness of breath.

The key to diagnosis is nephritic-pulmonary syndrome. The best initial test is the level of **antibasement membrane antibodies** to type IV collagen. The single most accurate test is lung or kidney biopsy, which will show linear deposits on immunofluorescence. Do **lung biopsy**, not renal, if there is pulmonary involvement.

Treatment is **plasmapheresis and glucocorticoids**. Cyclophosphamide may also help.

IgA nephropathy and **Henoch-Schönlein purpura** (HSP) have a common pathophysiology and renal presentation, but differ in that HSP also shows signs of systemic vasculitis.

IgA nephropathy (IgAN) is most commonly seen in Asian or native Americans age <35. It has 2 possible presentations:

- Mild or gross **hematuria appearing 1–2 days after a upper respiratory infection** (**most common on board exams**); resolves spontaneously in 30% of patients. (Compare this to poststreptococcal GN, where renal involvement occurs 1–2 weeks later or longer after a sore throat.)
- Hematuria and non-nephrotic proteinuria without infectious precedent which gradually progresses to end-stage renal disease (ESRD) (more insidious form)

Hypertension is common, as in most GN. About 40–50% of IgAN patients progress to ESRD. Renal biopsy shows proliferation with IgA deposits.

HSP has a similar presentation and biopsy, but also shows a skin rash or other vasculitic symptoms. Keys to diagnosis include hematuria, 1–2 day association with URI (for IgAN), and vasculitic rash, hematuria (for HSP).

Management. Renal biopsy is required if renal failure or proteinuria present. In HSP, skin biopsy is best.

Treatment. No proven treatment. In the presence of proteinuria, give ACE inhibitors/ARB. If nephrotic, try glucocorticoids.

Lupus nephritis is a constellation of glomerular diseases associated with SLE. There may be asymptomatic proteinuria or hematuria, nephrotic syndrome (secondary membranous GN), or severe nephritic syndrome with progressive renal failure eventually requiring dialysis. There are almost always other SLE signs or symptoms present, although a few patients present with renal signs only. Biopsy is key to planning therapy and prognosis.

Key to diagnosis: nephritic or nephrotic syndrome with SLE diagnostic criteria; best test is **double-stranded DNA levels** and low complement levels during disease flares. The most accurate test is a **biopsy**.

Treatment. Glucocorticoids with mycophenolate for severe proliferative disease (nephritic). Mycophenolate is superior to cyclophosphamide and has fewer side effects.

Idiopathic rapidly progressive glomerulonephritis (RPGN) presents with nephritic syndrome (occasionally nephrotic as well) and relentless subacute renal failure, with the serum creatinine rising over 1–2 weeks. An early renal biopsy is critical to diagnosis and shows epithelial cell crescents ("crescentic GN").

The key to diagnosis is rising creatinine; the best test is **renal biopsy.**

Treatment is glucocorticoids (start early to protect GFR) and cyclophosphamide (start after biopsy).

Clinical Recall

Which of the following is the most accurate diagnostic test for granulomatosis with polyangiitis?

A. Lung biopsy showing granulomas and eosinophils

B. Kidney biopsy showing linear deposits on immunofluorescence

C. Lung and nasal septum biopsy showing granulomas

D. Kidney biopsy revealing IgA deposits

E. Renal biopsy showing "humps" on electron microscopy

Answer: C

Note

IgA nephropathy is the most common primary GN worldwide.

Nephrotic Diseases

Nephrotic diseases are characterized by heavy proteinuria and may be primary or secondary to other systemic disease. They are often accompanied by a cluster of metabolic abnormalities (termed *the nephrotic syndrome*).

The nephrotic syndrome

The nephrotic syndrome is defined as the presence of GN sufficient to produce a level of **proteinuria >3.5 grams per 24 hrs, hyperlipidemia, edema, and low serum albumin**. Over 50% of nephrotic syndrome is associated with a systemic disease, esp. DM.

Proteinuria arises because the damaged glomerular basement membrane loses its negative charges; negatively charged albumin and key serum proteins then spill into the urine. This may lead to hypoalbuminemia and low serum oncotic pressure. Complications of the nephrotic syndrome include:

- Edema due to increased salt and water retention by the kidney, as well as low oncotic pressure in the serum
- Hyperlipidemia and increased atherosclerosis, most likely from the urinary loss of the lipoprotein markers or signals on the surface of chylomicrons and LDL that lead to the clearance of these lipids from the bloodstream
- Hypercoagulable states or thrombophilia, due to the urinary loss of natural anticoagulant proteins such as antithrombin, protein C, and protein S
- Spontaneous arterial or venous thrombosis due to hypercoagulability
- Iron, copper, and zinc deficiency may be present as a result of the urinary loss of their transport proteins such as transferrin and ceruloplasmin.

Diagnosis of nephrotic syndrome is based on the presence of **>3.5 gm per 24 hrs protein in the urine** (measured on 24-hour urine collection or a spot urine protein/creatinine ratio), low serum albumin, edema, and hyperlipidemia. The urinalysis will commonly only show 4+ protein, although some mild hematuria may be seen in several of the nephrotic glomerular diseases.

The key to specific diagnosis is **renal biopsy**. This may be deferred in diabetic nephropathy with a typical history.

Treatment. Control of the underlying disease, usually with glucocorticoids in the primary disorders. If steroids do not work, add cyclophosphamide or mycophenolate. Azathioprine may be useful. An ACE inhibitor or ARB is used for all patients with proteinuria, but they do not reverse the underlying disease. The following may also be helpful:

- Diuretics for edema
- ACE inhibitors/ARBs (equal efficacy) for control of proteinuria and hypertension
- Statins for hyperlipidemia
- Anticoagulation if DVT or PE ensues
- Good protein-calorie nutrition. Protein restriction is NOT indicated.

Note

Routine urine dipstick detects only albumin and not light chains or Bence-Jones protein (which must be done with urine immune electrophoresis). Lipiduria may lead to an appearance of "Maltese crosses" in the urine.

Primary nephrotic diseases

Focal-Segmental Glomerulosclerosis (FSGS). The most common cause of nephrotic syndrome in adults in the U.S. Secondary forms are seen with HIV (HIV nephropathy) and the use of heroin, as well as morbid obesity (possibly due to hyperfiltration).

Treatment: glucocorticoids (20–40% response); may progress to ESRD over 5–10 years

Membranous Glomerulopathy. Most are idiopathic (primary). Secondary forms associated with SLE, cancers such as lymphoma or breast cancer, infections such as endocarditis or chronic hepatitis B or C, and drugs such as NSAIDs, penicillamine, gold salts, and NSAIDs.

Treatment: glucocorticoids (30–50% response)

Minimal Change Disease. The most common nephrotic disease in children (90–95%); may account for 15% of adult disease. Usually primary, but NSAIDs and Hodgkin lymphoma have been associated with secondary disease. Light microscopy is normal and electron microscopy is needed to see fusion of foot processes.

Treatment: High glucocorticoid response, esp. in children. The disease is often treated in kids without biopsy, with biopsy reserved for non-responders. Adults are biopsied because of wider differential diagnosis.

Membranoproliferative GN (also see cryoglobulinemia in Nephritic Diseases). Now largely type 1, associated with chronic **hepatitis C** and B, with or without cryoglobulinemia and vasculitis. Renal presentation is **nephritic and/or nephrotic**. Shows low serum complement levels.

Secondary nephrotic diseases

Diabetic nephropathy is by far most common glomerular disease in developed countries. The incidence of nephropathy is directly proportional to the duration of the diabetes, and it normally appears as microalbuminuria after at least 10 years of type 1 or type 2 DM.

Microalbuminuria (50-300 mg/24 hours) is detected using the spot urine albumin/creatine ratio, NOT the routine urinalysis, which is insensitive to low degrees of proteinuria. Screen all diabetic patients annually for microalbuminuria. Following the appearance of microalbumin, the proteinuria worsens and eventually becomes nephrotic (>3.5 grams), followed by worsening renal function with rising serum creatinine. Over 5–10 years the patient progresses to dialysis-requirement or transplantation. The leading cause of death is cardiac disease due to accelerated atherosclerosis. Other complications include hyperkalemia and type IV renal tubular acidosis.

Keys to diagnosis include DM for at least 10 years; microalbuminuria or (later) nephrotic syndrome or decreased GFR. Although a renal biopsy is the most accurate test for renal involvement in diabetes, it is not routinely performed unless there is the possibility of another disease causing the renal failure.

Treatment includes tight control of diabetes and BP (<130/80 mm Hg); ACE inhibitor/ARB and statins for hyperlipidemia.

Renal amyloidosis occurs when amyloid proteins deposit in the glomerulus, causing damage to the GBM, leading to decline in GFR, albuminuria, and the nephrotic syndrome. There are 2 types of amyloidosis:

- **Amyloid light-chain** (AL): plasma cell dyscrasia causing deposition of protein derived from immunoglobulin light chains; may be associated with multiple myeloma
- **Amyloid A** (AA): amyloid is produced in association with a chronic infection, or rheumatoid diseases such as rheumatoid arthritis or IBD

Most patients will also have extrarenal manifestations:

- GI tract: diarrhea, malabsorption
- Heart: restrictive cardiomyopathy, rhythm disorders, and heart block
- ENT: large tongue (macroglossia)
- Neuro: carpal tunnel syndrome, peripheral neuropathy
- Muscles: weakness

The key to diagnosis is **biopsy of an involved organ** such as the fat pad, rectum, nerves, or kidney. Congo red testing shows green birefringence. Patients with AL amyloid will also have elevated urine, serum light chains typical of myeloma, and possible hypercalcemia.

Treatment is for the underlying malignancy or inflammation/infection. This is often very difficult. With AL amyloid, melphalan and prednisone can control protein production.

Other Glomerular Diseases

Several glomerular diseases cannot be categorized under the nephritic and nephrotic syndromes.

Hypertensive nephrosclerosis is the progressive chronic kidney disease associated with long-standing, poorly controlled hypertension. While previously a common cause of ESRD in the United States, it is now less so, due to more extensive treatment of hypertension. Patients' CKD is often attributed to "hypertension," when in fact the hypertension is secondary to a (potentially treatable) glomerular disease.

The renal pathology is characterized by non-immune, non-inflammatory glomerular sclerosis. If the hypertension is untreated, proteinuria and renal insufficiency progress gradually (over decades) to dialysis requirement. ACE inhibitors are the preferred antihypertensive due to their renal protective effect in CKD.

Alport syndrome is a glomerular disease due to genetic defect in type IV collagen, which structurally underlies the glomerular basement membrane. It is most commonly X-linked. Patients present with the combination of mild hematuria and proteinuria, along with ear (sensorineural hearing loss) and eye abnormalities. Men are more susceptible to disease, as they have a single mutated X chromosome. It may progress to dialysis-requirement. There is no treatment.

Hemolytic-uremic syndrome/idiopathic thrombocytopenic purpura (HUS/TTP) are thrombotic microangiopathies that may present with small platelet clots in the renal microvessels, causing secondary glomerular inflammation and renal failure. There is typically acute renal failure, mild hematuria, and low-grade proteinuria (non-nephrotic). Treatment is for the underlying disorder.

Table 8-5. Glomerular Diseases

Disease	Nephritic/ Nephrotic	Clinical	Serology Clue	Causes
Diabetic nephropathy	Nephrotic		Hgb A1c	DM
Membranous GN	Nephrotic			Cancer, Hep B/C, SLE, NSAIDs
Focal segmental glomerulosclerosis (FSGS)	Nephrotic			HIV
Minimal change disease	Nephrotic			NSAIDs
AA amyloidosis	Nephrotic	CHF, fractures		Chronic infections
AL amyloidosis	Nephrotic	CHF, fractures		Myeloma
Idiopathic RPGN	Nephritic	Rapid rise in creatinine		
Post infectious GN	Nephritic	1–2 weeks after infection	ASO, anti-hyaluronidase	Strep A, Staph
Membranoproliferative GN	Nephritic/ Nephrotic		Hep C/B tests	Hep C/B
Cryoglobulinemia	Nephritic/ Nephrotic	Purpura, neuro, joints	Serum cryos	Hep C/B
IgA nephropathy	Nephritic → Nephrotic	1–2 days after URI	IgA	Viral URI
Henoch-Schonlein Purpura	Nephritic	Purpura, GI, joints, abd pain	IgA	
Granulomatosis with polyangiitis (Wegener)	Nephritic	Lung, eye, UR, skin	c-ANCA	
Lupus nephritis	Nephritic	Skin, joints, heme	ANA, anti dsDNA	
Goodpasture	Nephritic	Hemoptysis	anti-GBM	
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)	Nephritic	Fever, lung, GI, cardiac, neuro, eye, skin	p-ANCA, eosinophilia	
Polyarteritis nodosa	Nephritic	Fever, eye, neuro, muscle, joints, GI	ESR	Hep B, IVDA
HUS (kids)		Hemolytic anemia, plats ↓		*E. coli*
TTP		Hemolytic anemia, plats ↓, + fever, neuro		
Hypertensive nephrosclerosis		Long hypertension		Long, severe HTN
Alport syndrome		Eye, ear defects		Genetic

END-STAGE RENAL DISEASE

Many chronic kidney diseases, if untreated or resistant to treatment, eventually lead to end-stage renal disease (ESRD). ESRD is characterized by severe reductions in the GFR and uremic symptoms requiring renal replacement therapy (dialysis or transplantation). In the United States the most common cause of ESRD requiring dialysis is diabetic nephropathy. (In some parts of Asia, IgA nephropathy is an equally common cause.)

Complications

Most complications of ESRD do not occur until GFR <20–30% of normal (25 mL/minute). A few complications (altered mental state, acidosis, hyperkalemia) are only seen when GFR <10%.

- **Metabolic acidosis** due to retained acids not filtered from the blood by the failing kidney. The anion gap is elevated. Treatment is dialysis.
- **Hyperkalemia** due to retained potassium not filtered by the failing kidney. This is a common cause of death in dialysis patients. Treatment is a low K diet and dialysis. Loop diuretics and GI binding agents (e.g., kayexalate) may be used prior to dialysis.
- **Hypermagnesemia.** Magnesium accumulates because the falling GFR decreases renal excretion. Treatment is restriction of magnesium intake, e.g., avoidance of milk of magnesia.
- **Hypocalcemia** due to the loss of 1,25-dihydroxy vitamin D production and from hyperphosphatemia (inability of the kidney to excrete phosphate). High phosphate levels contribute to low calcium levels by precipitating out in tissues in combination with the calcium. Treatment is reduction of phosphate and increase of calcium.
  - Hyperphosphatemia is treated with phosphate binders such as calcium carbonate or calcium acetate. Aluminum-containing phosphate binders should not be used, as aluminum is associated with CNS accumulation, dementia, and bone abnormalities. Sevelamer and lanthanum are phosphate binders that do not contain aluminum or calcium. Use when calcium is abnormally high due to vitamin D replacement.
  - Hypocalcemia is treated with 1,25 dihydroxy-vitamin D replacement.
  - Cinacalcet is a substance that simulates the effect of calcium on the parathyroid; it will tell the parathyroid to shut off parathyroid hormone production, thus helping to decrease phosphate. Use in severe, refractory cases.
- **Renal osteodystrophy** (osteitis fibrosa cystica). Bone abnormalities occur because chronic hypocalcemia leads to **secondary hyperparathyroidism**, which removes calcium from the bones. In addition, bones buffer the chronic acidosis ESRD by removing calcium from bone. Patients present with bone pain and fractures. Renal osteodystrophy is controlled with improving calcium and phosphorous levels and with cinacalcet. Parathyroidectomy may be needed for severe hyperparathyroidism that does not respond to medications.
- **Mental state changes.** A variety of cognitive and mood changes occur with uremia, normally only with severe CKD (GFR <10). The only treatment is dialysis.
- **Anemia** from the loss of production of erythropoietin from the kidney. The anemia is normochromic and normocytic. The anemia is treated with erythropoietin replacement, and iron replacement is often necessary when starting erythropoietin due to chronic losses from blood draws, dialysis, and malnutrition.

- **Bleeding.** The coagulopathy in ESRD arises from uremia-induced platelet dysfunction, which prolongs the bleeding time. Treatment is desmopressin, which releases subendothelial stores of von Willebrand factor and factor VIII, which increase platelet aggregation and adherence. A secondary cause in patients still making urine is nephrotic-syndrome associated loss of clotting factors in the urine.
- **Hypertension and accelerated atherosclerosis.** CKD leads to rapidly progressive coronary artery disease, which is the most common cause of death for those on dialysis. The reason for this is not clear. Treatment is good BP control (usually multiple medications and thorough dialysis) and statins for hyperlipidemia.
- **Pericarditis.** Caused by unknown uremic toxins; may or may not be an associated effusion. Requires urgent hemodialysis.
- **Infection.** ESRD patients are at increased risk of infection because neutrophils and other white cells do not work normally in a uremic environment. This is the second most common cause of death in dialysis patients. Vascular access infections (hemodialysis) and peritonitis (peritoneal dialysis) are common. The most common organism is *Staphylococcus* due to the frequent skin punctures required in dialysis.

Treatment

CKD is initially treated conservatively to minimize symptoms. However, when conservative management fails, renal replacement therapy is required. This can either be **dialysis** or **renal transplantation**.

Medical management of CKD includes restriction of fluids, potassium, sodium, protein, magnesium, and phosphate in the diet. Protein restriction is of **no value** and may be harmful. Common medications include erythropoietin, 1,25 dihydroxyvitamin D, phosphate binders, multiple antihypertensives, and furosemide (if patient still makes urine). Taking so many medications is very difficult for patients who often lack energy or who are confused.

Dialysis is used in patients with GFR <20%. (It is covered under Medicaid for all patients in the United States.) Dialysis options are hemodialysis and peritoneal dialysis.

Acute indications for dialysis are life-threatening abnormalities that require hospitalization:

- Pulmonary edema refractory to diuretics
- Hyperkalemia resistant to therapy
- Metabolic acidosis
- Pericarditis
- Altered mental state

Chronic indications for dialysis (usually initiated from the outpatient setting) include:

- Severe neuropathy such as myoclonus, wrist/foot drop
- Persistent nausea and vomiting
- Weight loss/malnutrition
- Bleeding diathesis
- Severe itching
- Fatigue not correctable with anemia correction

Overall, chronic hemodialysis is used in 85% of patients and peritoneal dialysis in 15%. Each can be done at home in properly trained patients.

The most common complications of dialysis are:

- Fluid overload
- Hypertension
- Post-dialysis orthostatic hypotension
- Dialysis access infections (peritonitis or AV access infection)
- Peritonitis (peritoneal dialysis)

Renal transplantation is the preferred treatment for ESRD patients requiring renal replacement therapy. All ESRD patients should be referred for transplant evaluation, ideally so they can be transplanted before dialysis is needed, but not all will qualify. The 5-year survival rate is by far superior with transplantation when compared with dialysis:

- Dialysis alone: 30–40%
- Diabetics on dialysis: 20%
- Live related donor: 72% at 5 years
- Cadaveric donor: 58% at 5 years

The average wait to obtain a kidney for transplantation is 2–4 years, and is becoming longer because of an insufficient donor supply.

Complications of transplantation include acute and chronic rejection, and infections due to immunosuppressive medications. Renal graft rejection is prevented by using cyclosporine, tacrolimus, corticosteroids, and mycophenolate. These are all medications that inhibit T-cell function.

Clinical Recall

Which of the following is not an indication for dialysis in ESRD?

A. Fluid overload refractory to diuretics

B. Severe metabolic acidosis

C. Uremic pericarditis

D. Severe hyperkalemia

E. Anemia

Answer: E

NEPHROLITHIASIS

Nephrolithiasis (kidney stones) is a conglomeration of insoluble minerals that form a stone. It can form in the collecting system of the kidney, descend down the ureter, and lead to obstruction.

All stones form more readily in concentrated urine, so volume depletion may precipitate them. There are also genetic predispositions to stone formation, sometimes linked to lack of stone-inhibiting proteins in the urine (e.g., nephropontin).

Types of stones include:

- Calcium oxalate (70%) and calcium phosphate (10%)
- Struvite/infection (Mg/aluminum/phosphate) (5–10%)
- Uric acid (5%)
- Cystine (1%)
- Indinavir

Kidney stones are a common cause of ED visits and are often severely painful.

Calcium Stones

Calcium stones (80% of all stones) have several risk factors:

- **Hypercalciuria**
  - Idiopathic renal hypercalciuria (normal serum calcium)
  - Resorptive from bone: hyperparathyroidism (10–30% of patients present with stones); multiple myeloma, metastatic disease to bone, hypercalcemia of malignancy (serum calcium high)
  - Increased GI calcium absorption: vitamin D intoxication; increased vitamin D with sarcoid and other granulomatous disease; familial (serum calcium high)
- **Hyperoxaluria**
  - Primary familial oxaluria
  - Enteric: with fat malabsorption as in Crohn disease, the fat binds to calcium, leaving unbound oxalate to be reabsorbed in increased amounts and then excreted into the urine.
- **Hypocitraturia**
  - Urine citrate is a stone inhibitor, binding with calcium. Patients with low urinary citrate have a higher risk for calcium stones. Patients with type 1 (distal) renal tubular acidosis often have hypocitraturia.

Struvite/Infection Stones

Chronic urinary infections with urease-producing organisms such as *Proteus*, *Pseudomonas*, and *Klebsiella* give a highly alkaline urine that leads to struvite (Mg/aluminum/phosphate) stones. These often produce large "staghorn" calculi filling the renal pelvis. The urinalysis may show characteristic "coffin lid" crystals.

Uric Acid Stones

Uric acid stones form in an acid environment and are associated with diseases that increase serum uric acid levels such as gout, hematologic malignancies, and Crohn disease. Unlike other stones, they are radiolucent on x-ray but can be seen on renal ultrasound.

Cystine Stones

Cystine stones (least common) are associated with the genetic disorder cystinuria. The urinalysis shows characteristic hexagonal crystals.

For **all stones**, patients present with constant flank or abdominal pain (not colicky) often radiating to the groin, and gross or microscopic hematuria. There is often associated nausea and vomiting, mimicking an acute abdomen or pelvic inflammatory disease. Gross hematuria is common. The patient may recall stone fragments in the urine.

Diagnosis. Best test is a radiologic test; both spiral helical CT scan (no contrast) and renal U/S are equally good. Urine testing may show:

- UA: blood, crystals; WBC, bacteria (infection stones)
- Electrolytes: high calcium, high oxalate, and/or low citrate (calcium stones); high uric acid (urate stones)
- pH: >8 in infection (struvite) stones, otherwise lower

Patients should strain their urine to catch a passing stone, which is then sent for analysis (best test for stone type). Serum studies include:

- Calcium (sometimes high in calcium stones); if elevated, check the parathyroid hormone level
- Uric acid (high in most urate stones)

Serum creatinine will be elevated only if there is bilateral obstruction (hydronephrosis), which would be seen on U/S or CT.

Treatment. Analgesia, hydration, and bed rest are the mainstays of treatment. Definitive treatment depends on stone size as determined by radiologic study:

- **<5 mm**: stones pass spontaneously
- **5–10 mm**: ureteral dilation agents, e.g., tamsulosin
- **1–2 cm**: lithotripsy (extracorporeal or transurethral)
- **>2 cm**: surgical excision (percutaneous or transurethral)

Recurrent stones should be treated with increased hydration—especially in warm climates—and medication appropriate to type.

- **Calcium stones**: thiazide diuretics (increases urine Ca reabsorption) or citrate if urine citrate is low
- **Urate stones**: allopurinol or febuxostat (lowers serum uric acid)

CYSTIC KIDNEY DISEASE

Cystic disease of the kidney may be primary or acquired. The most common primary disease is autosomal dominant polycystic kidney disease (ADPCKD), which often leads to ESRD and transplantation or dialysis. Acquired disease is most often seen in dialysis patients as an adventitious finding on CT scanning and requires no further management.

Autosomal Dominant Polycystic Kidney Disease

Autosomal dominant polycystic kidney disease (ADPCKD) is the most common cystic disease (prevalence 1:200 to 1:1,000). Presentation ranges from asymptomatic to painful to progressive CKD requiring eventual dialysis. Patients are commonly detected in early adulthood during evaluation for a urinary tract infection or flank pain, initially confused with stones.

Clinical presentation includes:

- Flank pain (one or both sides)
- Hematuria (microscopic or gross)
- Progressive loss of GFR
- Recurrent urine infections
- Hypertension
- Extra-renal manifestations: hepatic cysts (40–60%); intracranial aneurysm (10–20%); mitral valve prolapse (25%), colonic diverticula

Diagnosis. The best test is **renal ultrasound or CT scanning**. Many patients are concerned about the risk of rupture of undetected intracranial aneurysms. Without symptoms there is no recommendation to screen ADPCKD patients with cranial CT scanning, but this may be individualized for patient preference. Even if detected, there is no indication for neurosurgical intervention without evidence of a bleed.

Treatment is management of the complications (UTI, calculi, and hypertension) and prepare the patient for dialysis if renal function declines. There is no specific treatment. Some patients require nephrectomy for intractable pain.

Simple Cysts

Simple renal cysts are very common and usually of no significance. If they are smooth-walled with no debris inside the cyst, they can be managed without further treatment or diagnostic tests. If they have irregular walls or debris inside, follow closely with repeat scans to exclude malignancy.

HYPERTENSION

An estimated 50 million Americans have high BP. Hypertension may be primary (essential) or secondary to known diseases. Severe hypertension with end-organ damage is termed emergent hypertension.

Complications of uncontrolled hypertension include:

- **Cardiac:** increased risk of myocardial ischemia and infarction, left ventricular hypertrophy with eventual CHF, aortic aneurysm, and dissection
- **Cerebrovascular:** transient ischemic attack (TIA) or stroke
- **Renal**: nephrosclerosis with microscopic hematuria, mild proteinuria, progressive elevation of BUN/creatinine, and eventual dialysis. Hypertension worsens the prognosis of most renal diseases.
- **Retinopathy:** hemorrhages, exudates, arteriolar narrowing, and papilledema; these result in blurred vision, scotomata, and sometimes blindness

Essential Hypertension

Essential hypertension (>95% of all cases of hypertension) is best thought of as a syndrome with many causes, not a single disease. Causes in each patient vary: arterial stiffening, increased sodium sensitivity, or increased renin/angiotensin/aldosterone axis activity. This variability means that each patient will respond differently to a given intervention or medication.

Epidemiologically, essential hypertension is:

- More common with increasing age (found in 50% of those age >60)
- More common in obese patients
- Men > women until after menopause
- More common in black population at all ages, as is incidence of end-organ damage
- Onset usually age 25–55

Clinical Presentation. The most common presentation of essential hypertension is an **asymptomatic patient** in whom an elevated BP is found during a routine examination or evaluation for other medical problems. Much less commonly when symptoms are associated with hypertension, think of them as follows:

- Acute symptoms associated with a hypertensive emergency OR
- Complications from end-organ damage

With a hypertensive emergency, signs and symptoms may include evidence of stroke (neurologic findings, headache, blurred vision, dizziness) or cardiac symptoms (chest pain, dyspnea).

Diagnosis. Hypertension is diagnosed when **systolic BP 140 mm Hg** or **diastolic BP ≥90 mm Hg (or both) on repeated examination**. Systolic BP is particularly important and is the basis for diagnosis in most patients. These numbers apply to all adults age >18 (although for those age ≥80, systolic BP up to 150 mm Hg is now regarded as acceptable).

New 2017 ACC guidelines have recommended diagnostic values and therapy targets of **<130/80 mm Hg for patients with DM, elevated calculated cardiac risk (>10%),** or **chronic kidney disease**. These more rigid guidelines are controversial, since "tight" treatment increases medication use and increases the risk of falls, especially in elderly patients.

Table 8-6. ACC/AHA Guidelines (New as of 2017)

Normal BP	<120/80 mm Hg
Elevated	SBP 120–129 with DBP <80 mm Hg
Hypertension Stage 1	SBP 130–139 **or** DBP 80-89 mm Hg
Hypertension Stage 2	SBP >140 **or** DBP ≥90 mm Hg

As much as 20–25% of mild office hypertension is artifactual, i.e., these initial elevated readings merely represent a manifestation of anxiety on the part of the patient to the doctor/medical environment (known as "white coat hypertension"). These patients rarely have evidence of end-organ damage. Home BP monitoring is the best way around this difficulty, and all hypertensive patients should learn how to take and record their BP. Never label a patient as hypertensive after only a single reading: **repeat the reading 3–6 times over several months** before confirming the diagnosis and initiating therapy.

The physical exam includes evaluation of the heart for murmurs and LVH, auscultation for abdominal bruits seen in renal artery stenosis, and identifying edema seen in chronic kidney disease. A dilated eye exam looking for retinopathy is needed.

Lab testing is done to exclude chronic hypertensive complications and causes of secondary hypertension. Most routine lab testing will be normal. Once done on initial evaluation, repeat testing is unnecessary if the BP is well controlled, except to monitor drug side effects (e.g., hypokalemia with diuretics). Initial basic studies include:

- Urinalysis for protein, RBCs (screen for hypertensive nephrosclerosis and other renal diseases as secondary cause)
- Serum potassium (to exclude hyperaldosteronism as a secondary cause)
- Serum creatinine and BUN (screen for hypertensive nephrosclerosis and other renal diseases as secondary causes)
- Electrocardiogram to evaluate for left ventricular hypertrophy
- Serum glucose and plasma lipid analysis as an indicator of atherosclerotic risk

Treatment is aimed toward reducing BP to levels that will prevent acute and chronic complications. These targets vary depending on other patient risk factors.

- For patients **without** DM, cardiovascular disease, CV risk >10%, or chronic kidney disease, use the following guidelines:
  - Treat confirmed mild and moderate hypertension (DBP 90-100) with nonpharmacologic modifications in lifestyle: weight loss for the obese, dietary sodium restriction, aerobic exercise, reduced alcohol intake, and low-fat diet with increased dietary fiber (DASH "Dietary Approaches to Stop Hypertension" diet includes increased fruits/vegetables, low-fat dairy). For every kilogram of weight lost, there is generally a 0.5–1.0 mm Hg drop in systolic and diastolic BP. Relaxation methods have inconsistent effects.
  - Patients who continue to have diastolic BP >90 mm Hg after 3–6 months of nonpharmacologic therapy should then be started on an antihypertensive drug.

Note

First-line drugs for essential hypertension in patients without other diseases include thiazides, ACE inhibitors/ARB, and calcium channel blockers (CCBs). **Beta blockers should not be given**.

  - Treat severe hypertension (diastolic >100 mm Hg) immediately with drug therapy.
  - Use 2 medications as initial therapy for those with BP >160/100 mm Hg, since a single drug will not control this level of hypertension.
- For patients **with** DM, cardiovascular disease, elevated CV risk (<10%), or chronic kidney disease, treat more aggressively, with ≥1 medications, to achieve BP **both** SBP <130 mm Hg **and** DBP <80 mm Hg.

Medications. There are almost 50 medications approved for the initial treatment of hypertension, not including combination medications. Choice of drug is determined both by guidelines for the general population and by knowledge of drugs to use or avoid in specific patients based on their other medical problems.

Diuretics are still first choice in the absence of a specific indication or contraindication; their mortality benefit is unsurpassed, and chlorthalidone is best of all. If diuretics do not control the BP, add a second medication (an ACE inhibitor/ARB or CCB).

For BP >160/100 mm Hg, use a 2-drug combination: diuretic plus either ACE inhibitor/ARB or CCB.

Consider the following when treating specific hypertensive groups:

- Treat those who have post-myocardial infarction (ischemic heart disease) or systolic CHF with beta blockers.
- Treat those with systolic CHF or chronic kidney disease with ACE/ARB.
- Pregnancy: treat HTN with alpha-methyldopa, labetalol, hydralazine, or CCBs. **ACE inhibitors and ARBs are absolutely contraindicated.** Diuretics are relatively contraindicated.
- African-American patients receive the least BP lowering benefit from ACE inhibitors.

Clinical Recall

A 48-year-old man comes to the clinic with blood pressure 150/95 mm Hg. What is the best initial therapy?

A. Hydrochlorothiazide

B. Lifestyle modification and chlorthalidone

C. Lisinopril

D. Atenolol

E. Amlodipine

Answer: B

Secondary Hypertension

Secondary hypertension (5% of all HTN cases) is hypertension due to an identifiable underlying cause. Renal artery stenosis is the most common cause. The following groups should be screened for secondary hypertension:

- Those who become hypertensive age <25 **or** >55
- Those with a key feature of history, physical examination, or lab abnormality consistent with a particular form as described
- Those with "essential hypertension" who remain hypertensive despite increasing dosages and numbers of antihypertensive medications, i.e., those refractory to what should normally be effective therapy

With secondary hypertension, the presentation depends upon the cause.

- Renovascular disease causes an abdominal bruit
- Chronic kidney disease shows edema
- Cushing disease causes weight gain, moon-like facies, striae, and ecchymoses
- Primary hyperaldosteronism causes muscular weakness and polyuria/polydipsia from hypokalemia
- Pheochromocytoma (very rare) causes episodic hypertension associated with headache, palpitations, and sweating

The recommended lab work-up for essential hypertension will screen for the most common forms of secondary hypertension. A more intensive work-up can be done if there is a high clinical suspicion.

There are several types of secondary hypertension.

- **Renal artery stenosis** may be unilateral or bilateral and is caused by atherosclerotic disease in patients with high CV risk or fibromuscular dysplasia in young women. Physical exam may show an **upper abdominal bruit** radiating laterally (50–70% of patients). Radiologic confirmation tests include:
  - **Renal artery duplex U/S** (best screening test)
  - Captopril renogram measures the uptake of a radioisotope before and after the administration of captopril; a positive test is when there is decreased uptake of the isotope (i.e., decreased GFR) after giving the captopril (accuracy is diminished with renal insufficiency)
  - Magnetic resonance angiography (equal to sonography in diagnostic ability but more expensive)
  - Renal arteriography (more invasive and used prior to surgical revascularization to confirm the extent of stenosis)
  - **Treatment.** For **bilateral disease**, the best initial treatment is **percutaneous transluminal angioplasty** with stenting. If stenosis recurs, repeat the procedure. If angioplasty fails, attempt surgical revascularization. ACE inhibitors are effective for BP control; however, since they carry the risk of acute kidney injury in bilateral disease, use with caution.
  - For **unilateral disease**, it is not clear whether angioplasty is superior to ACE inhibitors.

- **Chronic kidney disease** (CKD) is typically associated with hypertension (often severe). Treatment emphasizes the use of ACE inhibitors (or ARB) for their effect in slowing progression of disease and reducing proteinuria. Once on dialysis, effective fluid removal will improve the resistant hypertension seen in these patients.
- **Primary hyperaldosteronism** is caused by a unilateral or bilateral adrenal adenoma (most common) or by bilateral adrenal hyperplasia. Cancer is rarely the cause. The key features are **hypertension in association with hypokalemia.** Diagnose with elevated aldosterone level and aldosterone/plasma renin activity in urine and blood. Treatment is surgical resection (for those with an adenoma) or potassium sparing diuretics such as spironolactone for those with adrenal hyperplasia. If an adenoma is suspected but not seen on radiologic studies, bilateral renal vein sampling for differential aldosterone levels may assist in locating the lesion.
- **Cushing disease** is hypercortisolism, most often due to ACTH hypersecretion by a pituitary adenoma. The key feature is hypertension in association with characteristic cushingoid manifestations such as truncal obesity, buffalo hump, menstrual abnormalities, striae, and impaired healing, etc. Dexamethasone suppression testing, 24-hour urine cortisol, or salivary cortisol are the best initial tests. Treatment is surgical resection of the adenoma.
- **Pheochromocytoma** (rare) is most often a benign tumor of the adrenal gland. The key feature is episodic hypertension in association with headaches, sweating, palpitations, tachycardia, or flushing (but only 50% have these acute features). The best initial tests are urinary vanillylmandelic acid (VMA), metanephrines, and free urinary catecholamines. Plasma catecholamine evaluation is helpful as well. CT and MRI will often localize the site of the tumor. Treatment is alpha-adrenergic blockade followed by surgical removal.
- **Coarctation of the aorta**: the key diagnostic feature is severe hypertension markedly greater in the upper extremities compared with the lower extremities.
- Other endocrine causes: oral contraceptives, acromegaly, and congenital adrenal enzyme deficiencies

Hypertensive Emergency

A hypertensive emergency (replaces the term *malignant hypertension*) is the acute onset of severe hypertension in association with severe and rapidly worsening symptoms of end-organ damage (~1% of hypertensive patients).

Clinical Presentation: Diastolic BP will usually be >120–130 mm Hg.

- **Neurologic:** encephalopathy, headache, confusion, seizures, subarachnoid or intracerebral hemorrhage
- **Cardiac:** chest pain, myocardial infarction, palpitations, dyspnea, pulmonary edema, jugular venous distension, gallops
- **Nephropathy:** acutely progressive hematuria, proteinuria, renal dysfunction
- **Retinopathy:** papilledema, hemorrhage, blurred vision

Lab evaluation is the same as for initial evaluation of essential hypertension, except that a head CT scan may be necessary to exclude hemorrhage. ECG is important as an initial test to exclude infarction.

Treatment. The initial goal is to reduce BP by no more than 25% within the first 1–2 hours.

- IV therapy is indicated: labetalol and nitroprusside are the best agents (nitroprusside carries a greater risk of thiocyanate toxicity when used >24 hrs)
- For those with myocardial ischemia or chest pain, nitroglycerin is indicated; other options are enalaprilat (an IV ACE inhibitor), esmolol, or nicardipine

The most important point in management is **not to lower the pressure too far** (e.g., not <95–100 mm Hg diastolic) so as not to compromise myocardial or cerebral perfusion.

Antihypertensive Medications

First-line agents

- **Thiazide diuretics**: **chlorthalidone** (preferred in guidelines), hydrochlorothiazide, metolazone, and indapamide are least expensive. Specific indications include CHF, edematous states, calcium kidney stones, nephrogenic DI. Side effects include decreased potassium and magnesium; increased glucose, calcium, uric acid, LDL; and gynecomastia. Relative contraindications include pre-diabetes and diabetes (worsens glucose tolerance), gout, hyponatremia, and hyperlipidemia.
- **ACE inhibitors** (ACEi): benazepril, enalapril, captopril, enalapril, lisinopril, quinapril, and ramipril
- **Angiotensin-receptor blockers** (ARBs): losartan, candesartan, valsartan, telmisartan, and irbesartan. Use only when intolerant of ACEi (more expensive). Specific indications for ACEi/ARB include chronic kidney disease, diabetics with microalbuminuria (to prevent nephropathy), CHF (afterload reduction), and postmyocardial infarction with low EF. Side effects include cough (ACEi only), angioneurotic edema (ACEi > ARB), neutropenia, hyperkalemia, taste disturbances, anaphylactoid reactions. Relative contraindications include hyperkalemia >5.0, bilateral renal artery stenosis (effective, but may cause AKI). Absolute contraindications include pregnancy.

Note

ARBs are less effective than ACEis in African-American patients.

Calcium channel blockers

- Dihydropyridines: amlodipine, felodipine, isradipine, nicardipine, nifedipine. Non-dihydropyridines: diltiazem and verapamil. Specific indications include angina pectoris (verapamil and diltiazem only), supraventricular arrhythmia, migraine, Raynaud phenomenon, esophageal spasm. Side effects include peripheral edema, constipation, heart block, reflex tachycardia (dihydropyridines). Relative contraindications include atrioventricular conduction defects, CHF from systolic dysfunction, angina pectoris, or CAD (dihydropyridines only).

Second- and third-line agents

- **Beta blockers** include bisoprolol (good in CHF, asthmatics), metoprolol (good in CHF, inexpensive) > acebutolol, atenolol, nadolol, pindolol, and timolol. Labetalol (combined beta and alpha) good for emergent hypertension. Specific indications include **myocardial infarction or ischemic heart disease (first line), diastolic and systolic CHF (first line)**, supraventricular arrhythmias including a-fib, migraine headache, glaucoma, and anxiety (resting tachycardia). Side effects include bronchospasm,

heart block, bradycardia, Raynaud phenomenon, depression, impotence, fatigue, decreased HDL, increased triglycerides, and hyperglycemia. Relative contraindications include asthma, COPD, atrioventricular conduction defects, CHF from systolic dysfunction, and diabetes because of masking signs of hypoglycemia; absolute contraindications include cardiogenic shock and acute asthma attack.

- **Potassium-sparing diuretics**: spironolactone, amiloride, and triamterene. Specific indications include edema, potassium wasting states (all), CHF (spironolactone), and cirrhosis (spironolactone). Side effects include hyperkalemia and gynecomastia (spironolactone). Relative contraindications include hyperkalemia >5 mmol/L. These agents are **often paired with thiazide diuretics**, neutralizing the thiazides' hypokalemic effect.
- **Loop diuretics** include furosemide, bumetanide, and ethacrynic acid. They are used for severe edema, especially pulmonary edema. Side effects include hypokalemia, hypocalcemia, and tinnitus.
- **Central-acting sympatholytics** include clonidine, guanfacine, guanabenz, and methyldopa. Clonidine can be useful in opiate detoxification. Side effects include depression, fatigue, dry mouth, impotence, bradycardia, heart block, and memory loss. Methyldopa gives hepatitis and Coombs-positive hemolytic anemia. Relative contraindications include elderly or depressed patients (orthostasis, falls, confusion).
- **Direct vasodilators** include hydralazine and minoxidil. Hydralazine is used in eclampsia and with nitrates for some patients with systolic CHF. Minoxidil is used topically to treat baldness. Side effects include a lupus-like syndrome (hydralazine) and marked fluid retention, pericardial effusion, and hirsutism (minoxidil). Relative contraindications include angina pectoris (reflex tachycardia).
- **Alpha-adrenergic blockers** include doxazosin, prazosin, and terazosin. They are used for those with lipid disorders (to reduce LDL and increase HDL), prostatic hyperplasia (to reduce obstructive symptoms), and nephrolithiasis (ureteral dilation). Side effects include syncope after the first dose, dizziness, and headache.

Note

Furosemide and other loop diuretics are the most potent agents for diuresis (CHF, renal failure), but they lack the vasodilating capability of thiazides so are **not effective for treating essential hypertension.**

FLUID AND ELECTROLYTE DISORDERS

The fluid and electrolyte disorders such as hyponatremia, hypernatremia, hypokalemia, and hyperkalemia are among the most common disorders seen in acute and hospital medicine.

Hyponatremia

Hyponatremia, a potentially lethal condition, is common in hospitalized patients. It is defined as a low serum sodium concentration <135 mEq.

The cause is almost always an excess of free water (some call it "hyper-aquemia"), usually by excessive renal water absorption.

The physiologic effects of hyponatremia do not stem from the sodium per se, but rather from the **low serum osmolality,** which causes cerebral edema. Sodium is the main determinant of the serum osmolality, as about 85–90% of sodium is extracellular. As seen in the formula for calculated osmolality, about 280 mosm/kg of the total serum osmolality of 290 mosm/kg comes from sodium.

$$\underset{290}{\text{Serum osmolality}} = \underset{280}{(2 \times \text{sodium})} + \underset{5}{\text{BUN}/2.8} + \underset{5}{\text{glucose}/18}$$

Therefore, **hyponatremia usually = hypo-osmolarity**.

While hyponatremia suggests a disorder of sodium, water is in fact the culprit, and total body sodium may be low, high, or normal. Hyponatremia can be classified by the patient's extracellular volume status (which equals the total body sodium):

- **Hypovolemic hyponatremia**: low extracellular volume (ECV), low total body sodium (dehydration, GI loss)
- **Euvolemic hyponatremia**: clinically normal ECV, normal total body Na (SIADH, thiazides, SSRIs)
- **Hypervolemic hyponatremia**: high ECV, high total body Na (cirrhosis, CHF)

While total body Na may be low, normal, or high, in all cases the **ratio of total body sodium to total body water** is low, therefore causing the hyponatremia.

Clinical Presentation and Diagnosis. Symptoms of hyponatremia are predominantly neurologic, ranging from mild confusion and forgetfulness, to disorientation and obtundation, to seizure (or even coma). Symptoms do not correspond to a specific sodium level because they largely depend on how fast the level dropped (but symptoms are rare, >125 mEq/L). An acute 15–20 point drop in sodium can cause a seizure or coma.

The history should focus on symptoms of malignancy, psychiatric, heart, renal, and liver disease. The drug history should ask about SSRI antidepressants, thiazides, and antipsychotics. The physical exam should determine the patient's **extracellular volume status** (especially orthostasis), hypotension, tachycardia, and edema.

Labs. In addition to the **serum sodium concentration**, the patient may benefit from checking serum osmolarity (usually low; if normal–high consider pseudohyponatremia), urine sodium (low [<10 mEq/L] in hypo- and hypervolemic types, high [>40] in euvolemic), and urine osmolarity (inappropriately high in face of low serum osmolarity, i.e. >200 mosm/kg, often >500 in SIADH).

Pseudohyponatremia

In pseudohyponatremia, serum sodium is low but serum osmolarity is normal or high. The patient appears euvolemic and is asymptomatic. No specific hyponatremia therapy is needed.

The common causes of pseudohyponatremia should be excluded before further work-up is done. These causes include **hyperglycemia** (where increased serum osmolarity pulls water out of cells, diluting the serum sodium) and **hyperlipidemia** (a lab artifact in which the high lipid fraction "dilutes" the measured sodium concentration despite a normal true serum value).

Hypovolemic hyponatremia

In hypovolemic hyponatremia, hyponatremia develops because of the loss of sodium and water through body fluids, but sodium losses exceed water losses. It may be worsened if pure water is used as fluid replacement, rather than balanced electrolyte solutions. For example, when you sweat during exercise (loss of hypotonic sodium and water) and replace only with free water, serum sodium may drop over time. Causes include GI loss (vomiting, diarrhea, gastric suction), skin loss (burns, sweating, cystic fibrosis), diuretics, and renal sodium loss (salt wasting in Addison disease, cerebral salt wasting after neurosurgical procedures).

Patients show signs of ECV depletion (orthostasis, hypotension, tachycardia, decreased skin turgor). Serum Na is usually >125 mEq/L, so hyponatremic symptoms are uncommon. Urine sodium concentration will be low (<10 mEq/L) reflecting avid renal Na reabsorption due to low ECV.

Treatment is normal saline (**the only time** this is used in hyponatremia).

Hypervolemic hyponatremia

In hypervolemic hyponatremia, hyponatremia is caused by high ADH levels, stimulated by a drop in "effective circulating volume", i.e., organ perfusion, such as in vasodilated states or CHF where cardiac output drops. The kidney reabsorbs sodium and water in response to the low perfusion, but more water is retained than sodium, leading to hyponatremia. Note that while Na and water reabsorption are usually linked in normal physiology, Na is controlled by aldosterone, water by ADH, so the linkage may not be precise in some patients with low effective circulating volume. This subset develops hyponatremia. Causes include CHF, nephrotic syndrome and low albumin states, and cirrhosis.

Patients will show signs of ECV expansion: edema, ascites, pulmonary crackles, and specific signs of heart, liver, or renal disease. The serum Na is usually >125 mEq/L, so hyponatremic symptoms are uncommon. Urine sodium concentration will be low (<10 mEq/L), reflecting avid renal Na reabsorption due to reduced renal perfusion.

Treatment is of the underlying disorder. Furosemide may help with urinary dilution, so enhance water excretion.

Note

End-stage kidney disease also may show hypervolemic hyponatremia, but from a different mechanism. Here, the failing kidney stops filtering water, yet the patient continues to drink it, leading to hyponatremia. This is often seen in patients prior to dialysis.

Euvolemic (normal ECV) hyponatremia

Patients with euvolemic hyponatremia are hyponatremic—often severely so—yet appear neither volume-depleted nor expanded. ADH levels are often very high. These cases often require specific hyponatremia treatment to avoid neurologic consequences. Causes include:

- High ADH levels released by the posterior pituitary
  - Psychiatric drugs and diseases (especially SSRI antidepressants, **most common cause** in United States)
  - Surgery, stress, endurance exercise ("marathon hyponatremia")
  - Hypocortisolism
  - Hypothyroidism
- ADH released by other body cells: syndrome of inappropriate antidiuretic hormone secretion (SIADH)
- Excess water intake: psychogenic polydipsia: patients must drink at least 15–20 liters a day of fluid to overwhelm the diluting capacity of the kidney
  - Decreased renal water excretion (non-ADH mediated)
  - Thiazide diuretics: inhibit distal tubule Na reabsorption and generation of free water, limiting ability of kidney to excrete very dilute urine
  - Often occurs in patients doing extreme hiking or exercise; patients on thiazides need to eat and/or drink solute solutions during such exercise

Diagnosis: Patients will show normal clinical volume status. While there is total body water expansion, water is an ineffective clinical volume expander, so no edema results. Serum Na varies, but may be very low (<110), so **hyponatremic symptoms are common**. Urine sodium concentration will be >40 mEq/L, reflecting the kidney's sensing of mild volume expansion from water retention, resulting in sodium diuresis, thus worsening the problem (water retention, sodium excretion). This explains the increased severity of hyponatremia in some patients. Urine osmolarity is often >500 mosm/kg, so administered fluids need to be more concentrated than that (i.e., avoid normal saline whose osmolarity is 300). Other lab work-up includes:

- Serum uric acid (low in euvolemic hyponatremia due to increased urine loss of UA)
- Serum ADH level: this is the single most accurate test, but is rarely done due to time and expense. Levels are high.
- Thyroid function (TSH) to rule out hypothyroidism
- Serum cortisol and/or ACTH stimulation test (rule out hypocortisolism)

Treatment. In general, patients should limit water intake since water will worsen any other cause. Conversely, solute intake should be increased. Marathon runners and endurance athletes should drink electrolyte beverages (not pure water) and eat regularly. Normal saline should be avoided since patients with this condition will absorb the water and dump the sodium, often worsening the hyponatremia. Medications suspected as causative should be stopped.

- For **symptomatic hyponatremia** (usually serum Na <120 mEq/L), administer hypertonic (3%) saline infusion (high sodium content, osmolality of 1000, much greater than what is exiting in the urine) and consider furosemide (helps dilute urine in euvolemic hyponatremia). Stop acute treatment when the patient becomes asymptomatic (usually when Na >120 mEq/L). Monitor the rate of rise of sodium so as not to cause **central demyelinating syndrome**, which occurs if sodium is corrected too rapidly or is overcorrected. Generally, the rate of rise should not exceed 0.5–1 mEq per hour; this means no more than a 12-point rise in 12–24 hours.
- For **moderate asymptomatic hyponatremia** (usually serum Na >120), increase serum Na slowly. **Educate the patient about limiting water intake**. Also consider ADH antagonists (tolvaptan, conivaptan), demeclocycline (mild ADH antagonist), urea or salt tablets (increase solute without water), or fludrocortisone (used for cerebral salt-wasting after neurosurgery).

Note

Hyponatremia can be corrected as rapidly as 2 mEq per hour if the patient is seizing.

Hypernatremia

Hypernatremia is the "flip side" of hyponatremia, and is caused by **free water deficiency**. Causes include non-renal losses (GI, sweating) (**most common**) or DI, where a lack of ADH (or resistance to it) causes persistent polyuria and free water loss.

Non-renal water loss is often seen during summer months, when temperatures rise. Symptoms include low urine output and concentrated urine. Causes include:

- Insensible losses: sweating, burns, fever, exercise, or respiratory infections
- GI loss: osmotic diarrhea (e.g., lactulose, malabsorption), some infectious diarrhea
- Transcellular shift: rhabdomyolysis or seizures causing muscles to avidly take up water from the ECV

Note

A critical cause in the development of hypernatremia is **lack of water intake**, usually due to trauma, environmental causes (lost in the desert), or mental status changes. It is also seen in patients with DI who are placed NPO in the hospital for surgery and cannot drink their usual liters of water per day.

Renal water loss may be caused by renal ADH resistance (nephrogenic DI), inadequate ADH release from the posterior pituitary (central DI), or drug-induced loss of excess free water. Symptoms include high urine output and dilute urine.

- Nephrogenic DI: **lithium, chronic interstitial renal disease**, hypercalcemia, hypokalemia, sickle cell disease
- Central DI: Idiopathic (most common); **brain surgery**, trauma, infection, tumor, granulomatous, or hypoxia
- Osmotic diuresis with renal water loss: diabetic ketoacidosis (DKA), nonketotic hyperosmolar coma, mannitol, loop diuretics (water lost > sodium)

Clinical Presentation and Diagnosis. Symptoms are primarily neurologic. With severe hypernatremia of any cause, lethargy, weakness, irritability, seizures, and coma are present. There should be a history of limited water access (e.g. loss of consciousness, confusion, falls, lack of water access), since patients with these diseases will normally drink enough water to keep their serum sodium normal.

The physical exam usually demonstrates signs of volume depletion (orthostasis, tachycardia), since water and salt are both lost. Urine output is <1 liter per day in insensible water loss, while 3–20 liters per day in diabetes insipidus.

Lab evaluation will show high serum Na, low urine Na (<10 mEq/L).

- In DI, the urine osmolality will often be <100 mosm/kg, reflecting the dilute urine.
- To **differentiate central from nephrogenic DI**, administer ADH (nasal, IV). The urine osmolality will increase in central DI, but not in nephrogenic DI.

Treatment. Stop or reduce the lithium or other implicated medication. If patients are alert, they can drink water. If patients are hypovolemic (tachycardia, orthostasis), first administer normal saline and then switch to hypotonic saline (0.45% saline or 5% dextrose in water). Once they become alert, switch to oral fluids.

- Correction of sodium should be **<1 mEq/L every 2 hours** or **12 mEq/L per day**. Complications of overly rapid correction include cerebral edema and seizures, possibly causing permanent neurologic damage. A rate of correction as fast as 2 mEq per hour is acceptable only if the patient is seizing.
- In **central DI also use vasopressin** (ADH) subcutaneously, intravenously, intramuscularly, or by nasal spray. Central DI is usually transient, esp. post operatively
- In **nephrogenic DI**, reduce or stop the causative drug. For chronic DI, thiazides may be useful (recall that they **cause** hyponatremia but **treat** hypernatremia). NSAIDs may also help, as they inhibit prostaglandins which impair concentrating ability; NSAIDs will increase the action of ADH at the kidney.

Hypokalemia

Hypokalemia (serum potassium <3.5 mEq/L) is relatively common, especially in patients taking diuretics or with poor PO intake. Dietary potassium is high in fruits and meats. Excretion is by renal (controlled by aldosterone) and GI routes.

Unlike most electrolytes, potassium is mainly intracellular, so serum levels may not accurately reflect total body levels. Shifting of K in and out of cells is a major determinant of the serum concentration, in addition to total body K.

Hypokalemia may be caused by the following:

- **K shifting into cells:** beta agonists, insulin, metabolic alkalosis
- **Low K intake:** alcoholism, starvation
- **GI losses:** diarrhea
- **Renal losses**: from diuretics; low magnesium; increased aldosterone states (e.g., hyperaldosteronism, Bartter syndrome, or Cushing disease); vomiting (urine loss of K stimulated by high aldosterone and urine loss of bicarbonate)

Clinical Presentation. Symptoms and signs of hypokalemia predominantly affect the muscles and the heart.

- Muscle weakness, paralysis (when it is severe), and rhabdomyolysis
- Cardiac arrhythmias (which can be fatal)
- Nephrogenic diabetes insipidus: potassium is necessary for ADH effect on the kidney

In emergency cases, the most important diagnostic test is the **ECG**; abnormalities will include T-wave flattening and U-waves.

Treatment. Correct the underlying cause. Replete potassium as follows:

- Oral: the gut regulates absorption, i.e., there is no maximum rate of oral potassium replacement.
- IV: maximum 10–20 mEq/hour; do not use dextrose containing fluids as they increase insulin release and lower the serum potassium. Too-rapid IV repletion may cause a **fatal arrhythmia**.

Very large amounts of potassium may be necessary to raise the body potassium level by even 1 or 2 points. The best estimate is to give 4–5 mEq per kg per deficit point.

Hyperkalemia

Hyperkalemia (serum potassium >5.5 mEq/L) is common in patients with DM and chronic kidney disease. It is potentially lethal and requires prompt treatment and good prevention. Patients at risk should avoid bananas, citrus, and other high-K foods. Causes include:

- Increased intake (orally or by IV): usually in the presence of impaired excretion
- Shift of K out of cells into ECF:
  - Pseudohyperkalemia (a lab artifact): secondary hemolysis due to mechanical RBC trauma during venipuncture (look for "hemolyzed" specimen)
  - Excessive thrombocytopenia >1,000,000, leukemia (WBCs >100,000)
  - Damaged cells: rhabdomyolysis, seizures, extreme exercise
  - Metabolic acidosis: H+ moves into cells, K+ moves out; for every 0.1-point decrease in the pH, potassium level will increase by 0.7

Note

Hyperaldosteronism can be caused by adrenal adenomas (low renin and AT), bilateral adrenal hyperplasia (low renin and AT), or renal artery stenosis (high renin and AT). Hyperaldosteronism causes secondary hypertension, hypokalemia, and metabolic alkalosis.

Note

A U-wave is an extra wave after the T-wave that is indicative of Purkinje fiber repolarization.

  - Insulin deficiency (type 1 diabetes, DKA)
  - Periodic paralysis: mild, brief episodes of muscle weakness with mild increase in K+; diagnosis with recurrent attacks and family history
- Decreased urinary K excretion
  - Chronic kidney disease with GFR <10% normal
  - Potassium-sparing diuretics: amiloride, triamterene, spironolactone
  - ACE inhibitors and ARBs
  - Type IV RTA
  - Hypoaldosteronism: DM (hyporeninemic), Addison disease, adrenalectomy, adrenalitis, adrenal enzyme deficiency, heparin (inhibits production of aldosterone)
  - NSAIDs

Clinical Presentation. Patients are often asymptomatic despite dangerous hyperkalemia. Muscular weakness is seen with serum K+ level >6.5. The most important initial test is the **ECG.** Abnormal cardiac conduction is the most common cause of death. With worsening hyperkalemia, the ECG shows:

- Peaked T waves
- Flattening of P waves
- Widened QRS and short QT
- Flattening of QRS complexes
- Ventricular fibrillation or tachycardia

Treatment. For asymptomatic patients with normal ECG: Low K diet; diuretics and/or GI binding agents (Kayexalate, patiromer). Patiromer is a newer GI binding agent with fewer GI side effects (including bowel necrosis) than Kayexalate.

For patients with ECG changes, urgent treatment is required. The serum K may be lowered rapidly, but hypokalemia should be avoided. A stepwise approach should be taken. In practice, the steps are often done simultaneously, as some drugs take time to work.

1. First, stabilize the cardiac membrane. Calcium gluconate: membrane stabilization (most emergent treatment in presence of ECG abnormalities); effect is immediate and short-lived
2. Next, shift the K intracellularly
   - Glucose and insulin: drives K+ intracellular, takes 30–60 min to work
   - Beta agonists (e.g., albuterol)
3. Then remove K from the body
   - Loop diuretics (ineffective in some patients with CKD, low GFR)
   - GI cation exchange resin (Kayexalate or patiromer)
     - Patiromer has lower incidence of bowel necrosis
     - Resin absorbs 1 mEq K+ per g and releases 1 mEq Na+
     - Give with sorbitol to prevent constipation
     - Kayexalate available as retention enema for those who cannot take orally
   - Dialysis if above fail or if an ESRD patient

Clinical Recall

Which of the following treatments for hyperkalemia removes potassium from the body?

A. Calcium chloride

B. Sodium bicarbonate

C. Potassium exchange resin

D. Beta agonists

E. Insulin

Answer: C

ACID/BASE DISTURBANCES

Acid/base disorders are common and are often seen in hospitalized patients as a consequence of serious illness and medications. They have consequences and sequelae based on changes to the body pH, but also are very useful diagnostically as clues to other diseases.

- **Acidemia** and **alkalemia** are reduced and increased blood pH, due to ≥1 causes.
- **Acidosis** and **alkalosis** are specific pathologic processes (≥1) that cause the net change.
- A **mixed acid-base disorder** means having ≥2 acidoses/alkaloses, e.g., an anion gap metabolic acidosis with a respiratory alkalosis (as in aspirin toxicity).
- A **compensation** is not a disorder; it is the body's normal response to a change in pH caused by an alkalosis or acidosis. For example, during a metabolic acidosis (e.g., DKA), the acidemic pH is sensed by the CNS, which induces pulmonary hyperventilation (the respiratory compensation), lowering the pCO_2 and raising the pH back toward normal. Each acid base disorder has an expected compensation.

Metabolic Acidosis

Metabolic acidosis is a decrease in blood pH [<7.35] caused by either endogenous or exogenous acids accumulating in the blood. It often accompanies serious illness (e.g., lactic acidosis in sepsis).

The pattern seen on the arterial blood gas is:

pH	pCO_2	HCO_3^-
↓	↓	↓

The low bicarbonate reflects the increased serum protons, which lowers the pH. The pCO_2 then falls as a **respiratory compensation**, as the CNS senses the acidosis and stimulates hyperventilation, which raises the pH back toward normal. Note that this reduction in pCO_2 is **not a "respiratory alkalosis"** (which would suggest an actual respiratory disorder, not a compensation as seen here).

The expected compensation for a given level of HCO_3 in metabolic acidosis can be predicted from Winters Formula:

$$\text{Expected } PaCO_2 = (1.5 \times \text{serum } HCO_3) + 8 \text{ mm Hg } (\pm 2)$$

If the observed pCO_2 is too high or too low compared to this calculated value, a second acid-base disturbance is present (see Mixed Acid Base Disorders).

An alternative shortcut (but less accurate) is that in metabolic acidosis the expected $PaCO_2$ is approximately equal to the last 2 digits of the pH ± 2.

Formulas such as these become less accurate at extremes of pH. For these, use an acid base nomogram.

The **anion gap** should be calculated once the diagnosis of metabolic acidosis is established so that we can categorize metabolic acidoses into high anion gap or normal anion gap types. The **anion gap** is an estimate of the unmeasured anions present in the bloodstream. The blood is electrically neutral, with a mix of anions and cations that include minerals (Na^+, H^+, Ca^{++}, HCO_3^-), proteins (albumin [negative charge]), and immunoglobulins (positive charge). Rather than measure them all, the anion gap is used to estimate the net charge due to abnormal anions or cations that may be present in the blood.

$$\textbf{Anion gap} = \textbf{(Na+)} - \textbf{(}HCO_3\textbf{}- + Cl^-\textbf{)}$$

(normal 8–12)

The normal anion gap of 8–12 means that in normal subjects all the anions, cations, and proteins that are **not** Na^+, HCO_3^-, or Cl^-, add up to a net negative 8–12 mEq/L. When this number increases (becomes more negative), it indicates an "anion gap" caused by excess anions that are **not normally present in the blood**. These may be exogenous (e.g., oxalic from antifreeze) or endogenous (lactic from sepsis).

Therefore, when there is an elevated anion gap, assume that a **high anion gap acidosis** is present. If instead the patient has a metabolic acidosis with a normal anion gap, a **normal anion gap metabolic acidosis** is present.

Clinical Presentation and Treatment. Patients with metabolic acidosis will have symptoms related to the underlying cause. Acidemia per se does not cause symptoms until very severe (<7.1), when it may cause arrhythmias and decreased cardiac output. Treatment varies by cause, and usually includes some combination of removing the excess acid and administration of bicarbonate.

Note

The anion gap may become abnormally low without acid-base abnormalities due to excess blood cations or deficient anions:

- Hypoalbuminemia (cirrhosis, nephrotic syndrome)
- Multiple myeloma (excess positive light chains)
- Lithium (excess cations)

High anion gap metabolic acidosis

This is a metabolic acidosis caused by excess acid present in the blood, which may be endogenous or exogenous (ingested). The main causes are summarized (note that many of these cause lactic acidosis, which can be measured in routine lab testing).

Use the mnemonic **MUDPILES**:

- **M**ethanol, metformin (cause formic acidosis and lactic acidosis, respectively)
- **U**remia (GFR <10% of normal)
- **D**iabetic ketoacidosis (DKA): beta hydroxybutyric acid and acetoacetate
- **P**ropylene glycol (causes lactic acidosis)
- **I**NH (cause lactic acidosis)
- **E**thylene glycol, ethanol (cause oxalic acidosis and ketoacidosis, respectively)

- **L**actic acid: sepsis, shock, ischemia, drugs, etc.
- **S**alicylates: aspirin overdose (causes lactic acidosis with combined respiratory alkalosis)

Clinical Presentation varies depending on the cause:

- Methanol: altered mental state, blindness, renal failure
- Uremia: edema, elevated serum creatinine
- Diabetic ketoacidosis (DKA): elevated serum and urine ketones, hyperglycemia, hyperkalemia
- Ethylene glycol: altered mental state, vomiting, hypocalcemia, oxalate crystals in urine, elevated serum osmolality
- Ethanol: vomiting, withdrawal, urine and serum ketones
- Lactic acid: hypotension, fever, causative drugs (metformin, INH, propylene glycol, aspirin); high serum lactic acid level
- Salicylates: tinnitus, nausea, respiratory alkalosis (mixed disorder); high serum lactic acid level

Treatment. Remove the offending acid or prevent its formation. Specific treatments include:

- Dialysis: uremia, methanol, ethylene glycol, propylene glycol, severe aspirin
- Saline and insulin: diabetic ketoacidosis
- Sodium bicarbonate: aspirin, methanol, ethylene glycol, propylene glycol
- Fomepizole: ethylene glycol, methanol (prevents conversion of substrate to toxic acid)

Normal anion gap metabolic acidosis

Metabolic acidosis with a normal anion gap results from either loss of bicarbonate (renal, GI) or deficient renal excretion of acid (renal tubular acidosis).

The kidney normally excretes metabolic acids by secreting protons in the cortical collecting duct (controlled by aldosterone), which are then buffered and excreted by either of the following:

- Filtered buffers (phosphate) called *titratable acid*: reduced when GFR drops (chronic kidney disease)
- Ammonia, secreted in the proximal tubule (regulated by serum pH): increased by acidosis and reduced by hyperkalemia

The main causes of normal anion gap metabolic acidosis are:

- **GI loss of bicarbonate:** Diarrhea and any post-surgical state that causes increased fecal transit may cause non-gap metabolic acidosis, due to loss of bicarbonate. Hypokalemia is usually present due to simultaneous GI potassium loss. The kidney functions normally, excreting acid and lowering pH to <5.5.
- **Proximal (type I) renal tubular acidosis:** This is an inability of the principal cells in the cortical collecting duct to secrete protons, a step needed for net acid excretion. It may be due to a transporter malfunction or to a back-leak of secreted protons back through damaged luminal cell membranes (as in amphotericin toxicity). Causes include chronic renal interstitial disease, Sjogren syndrome, SLE (and other autoimmune diseases), lithium, and amphotericin B.

Diagnosis: Serum HCO_3 drops modestly, usually to 18–20 mEq/L. Serum K is low. Urine pH is appropriately low (<5.3) for any acidosis, unless the patient has just ingested bicarbonate, in which case the transient bicarbonate diuresis will raise the urine pH.

To confirm diagnosis, show that bicarbonaturia develops with bicarbonate administration, even when the patient is acidotic. Normal subjects do not excrete bicarbonate in the urine until their serum bicarbonate >24.

Treatment is bicarbonate (large amounts), potassium, and thiazide diuretics.

Distal (type II) renal tubular acidosis

This may be an isolated inability of the proximal tubule to reclaim bicarbonate, or accompanied by global proximal tubule dysfunction (Fanconi syndrome)—the latter would also show glucosuria, phosphaturia, uric acid, and aminoaciduria. The loss of bicarbonate leads to the non-anion gap metabolic acidosis. Patients may develop **osteomalacia**. Causes include multiple myeloma, amyloidosis, and genetic disorders such as cystinosis and galactosemia.

Diagnosis. Serum HCO_3 may drop to low levels (<15). Serum K is usually low but can vary. Urine pH is inappropriately high (>5.5) for acidosis, due to the lack of free protons secreted into the tubule. There may be associated nephrocalcinosis or renal stones. Associated hypocitraturia may lead to calcium renal stones.

Treatment is bicarbonate and citrate.

Hyperkalemic (type IV) renal tubular acidosis

Hyperkalemic (type IV) RTA (most common RTA) is especially common in diabetics. Its name is a clue to the pathophysiology:

- The initial problem is chronic **hyperkalemia**, often due to hyporeninemic hypoaldosteronism (a common consequence of DM, where patients lack sympathetic regulation of renin).
- The hyperkalemia inhibits the proximal tubule's secretion of ammonia.
- The lack of ammonia limits net acid excretion and causes the acidosis.

Causes (and factors that worsen it) are largely those of hyperkalemia:

- DM (with hyporeninemic hypoaldosteronism) (50%)
- Adrenal insufficiency with mineralocorticoid deficiency
- ACE inhibitors/ARB: reduce aldosterone
- K sparing diuretics: raise serum K
- Sickle cell disease

Note

Urine anion gap (urine Na + K – Cl) estimates the ammonium secreted in the urine, so it can help detect RTAs. A **negative gap** indicates ammonium is **present**, and a positive gap indicates ammonium is not present. Ammonium is the normal renal response to acidosis, so it should be present unless there is an RTA.

- Diarrhea: UAG negative (ammonia present)
- Distal RTA: UAG positive (ammonia absent)
- Type IV RTA: UAG positive (ammonia absent)

Diagnosis. Serum HCO_3 only drops to a moderate level (18–22). The hyperkalemia is uniform. Urine pH is appropriate (<5.3) for acidosis, since distal proton secretion is normal.

Treatment. Lower serum potassium (diet, change medications, diuretics). Add bicarbonate and fludrocortisone (if aldosterone deficient) but use caution because it causes edema.

Table 8-7. Renal Tubular Acidosis

Type	Associations	Serum HCO_3^- (mEq/L)	Serum K	Urine pH	Bones and calcium
Proximal (Type II)	Myeloma, acetazolamide, Fanconi syndrome	18–22	low	<5.3	Osteomalacia
Distal (Type I)	Lithium, amphotericin, rheumatoid disease	12–20	low	>5.5	Calcium stones, nephrocalcinosis, low urine citrate
Type IV	DM	18–22	high	<5.3	None

Metabolic Alkalosis

Metabolic alkalosis is an increase in blood pH (>7.45) caused by loss of body acids (vomiting) or gain of bicarbonate. Because excess bicarbonate is normally excreted rapidly by the kidney, maintenance of metabolic alkalosis usually requires concurrent **volume depletion**, which stimulates Na and HCO_3 reabsorption.

The pattern seen on the ABG is:

pH	pCO_2	HCO_3^-
↑	↑	↑

The respiratory compensation is respiratory—a central hypoventilation, raising pCO_2 and returning the pH toward normal. Hypokalemia is seen in most cases, and K depletion compounds the alkalosis and needs to be corrected to cure the acid base disorder.

Metabolic alkalosis is often classified by **responsiveness to saline infusion**, which is predicted by measuring the **urine chloride concentration**. Those with low urine chloride (e.g., vomiting, volume depletion after diuretics) will correct with saline. Those with a high or normal urine chloride (e.g., hyperaldosteronism) will not. The saline-responsive group is by far the most common.

- Saline-responsive metabolic alkalosis (low urine Cl^-)
  - GI loss (vomiting, nasogastric suction)
  - Diuretics

Note

Type IV RTA (most common RTA) always shows concurrent hyperkalemia and should be looked for in diabetic patients.

Note

In **diuretic use**, patients are saline responsive but urine chloride is variable.

- It may be high if the patient is still taking the diuretic.
- It may be low if the patient has stopped the diuretic but is still volume-depleted.

- Saline-resistant metabolic alkalosis (high-normal urine Cl^-)
  - Hyperaldosteronism (including Cushing Syndrome)
  - Exogenous steroids
  - Tubular diseases causing K loss (Liddle, Gitelman, Bartter syndromes)
  - Excess bicarbonate administration

Clinical Presentation. Hypokalemia is seen in all the conditions. More specific findings include:

- Saline responsive: volume depletion (orthostasis, tachycardia)
- Saline-resistant: hypertension (in hyperaldosteronism, Cushing, and Liddle syndromes)

Treatment. Potassium repletion for all forms. Saline-responsive alkalosis should receive oral or IV saline to expand the ECV. The endocrine-related saline-resistant causes require treatment of the underlying disorder. Those with high aldosterone may respond to spironolactone.

Respiratory Acidosis

Respiratory acidosis is a decrease in blood pH (<7.35) caused hypoventilation with CO_2 retention. This can be acute or chronic, and due to problems with nervous control of breathing, muscle strength, or intrinsic pulmonary disease. The pattern seen on the ABG is as follows:

pH	pCO_2	HCO_3^-
↓	↑	↑

Note

Severe metabolic alkalosis will enhance calcium binding to albumin, reducing the free (ionized) calcium level, potentially causing hypocalcemic symptoms even with a normal total calcium concentration.

The metabolic compensation is initially the intracellular buffering of protons, then enhanced renal bicarbonate reabsorption, both causing serum HCO_3^- to rise, thus returning the pH toward normal. Causes include hypoventilation of any cause:

- **CNS/Neurological**: opiates; barbiturates/other sedatives; Pickwickian syndrome; sleep apnea; morbid obesity; neuropathy
- **Lung parenchymal disease or pleural disease**: COPD; severe asthma; pleural effusion; aspiration
- **Respiratory muscle weakness**: myopathies; myasthenia gravis; kyphoscoliosis

Clinical Presentation and Diagnosis. Evaluation should initially be directed to an immediate reversible cause, especially opioid overdose. Naloxone should be given unless a clear alternative explanation is present. Other labs include urine or serum toxicology and chest x-ray.

Treatment. Naloxone in uncertain cases; endotracheal intubation if the hypoventilation worsens; draining of pleural effusions

Respiratory Alkalosis

Respiratory alkalosis is an increase in blood pH (>7.45) caused by hyperventilation, which lowers the pCO_2. It can be acute or chronic, and due to psychiatric, pain syndromes, or pulmonary disease.

pH	pCO_2	HCO_3^-
↑	↓	↓

The metabolic compensation is initially due to intracellular buffering, then enhanced renal bicarbonate excretion, both causing the HCO_3^- to fall, thus returning the pH toward normal.

Since hyperventilation is a normal response to hypoxemia, first check the arterial O_2 saturation by pulse oximetry to guide further evaluation.

Hypoxic causes (low pulse oximetry O_2)

- **Hypoxic causes** (low pulse oximetry O_2): asthma; pneumonia; pulmonary embolus (not always hypoxic); sarcoidosis; high altitude
- **Nonhypoxic causes:** anemia (although total O_2 capacity is reduced); anxiety; pain; aspirin toxicity (mixed disorder, precedes the metabolic alkalosis); pregnancy
- Cirrhosis

Clinical Presentation and Diagnosis. Initial evaluation should include pulse oximetry; oxygen should be supplied if patient is hypoxic. Pulmonary embolus should be ruled out in uncertain cases. Other labs include CBC (anemia evaluation) and chest x-ray.

Treatment. Oxygen and support for the specific disorder; acetazolamide (carbonic anhydrase inhibitor, stimulates renal bicarbonate excretion) for headaches and nausea caused by high altitude respiratory alkalosis

Mixed Acid-Base Disorders

Acid-base disorders may not come alone as a single disorder; in other words, patients may develop 2 or more, and the net blood pH reflects the combination of all of them. An example is aspirin toxicity, where there is a combined respiratory alkalosis and high anion gap metabolic acidosis. The net pH may be normal in the face of abnormal pCO_2 and bicarbonate, as shown by these values: blood: pH 7.41, pCO_2 25 mm Hg, HCO_3 16 mEq/L.

Diagnosis. There are several clues to help identify a mixed acid-based disorder:

- **Clue 1**: If there are large changes in pCO_2 and HCO_3 but a near-normal pH, there is a mixed disorder (as shown in the aspirin toxicity example).
- **Clue 2**: In **all single disorders**, the **pCO_2 and HCO_3 "move together"**; both either go up or down. If they go in different directions or if one is normal, suspect a mixed disorder.
  - Suppose the values from a patient after cardiac arrest are blood pH 7.15, pCO_2 60 mm Hg, and HCO_3 20 mEq/L. The pCO_2 is elevated while the bicarbonate is depressed, which violates the "move together" rule.
  - Therefore, the patient has a combined metabolic and respiratory acidosis, typical of those who have had a cardiac arrest. The severely acidemic net pH further supports this.

Table 8-8. Simple Acid Base Disorders

	pH	pCO_2	HCO_3^-
Metabolic acidosis	↓	↓	↓
Metabolic alkalosis	↑	↑	↑
Respiratory acidosis	↓	↑	↑
Respiratory alkalosis	↑	↓	↓

- **Clue 3**: A more refined way to diagnose mixed disorders is to use compensation formulae. In simple disorders, the calculated expected value should align with the measured value. The Winter's Formula (for metabolic acidosis compensation) is an example:

$$\text{Expected } PaCO_2 = (1.5 \times \text{serum } HCO_3) + 8 \text{ mm Hg } (\pm 2)$$

Suppose the values from a septic patient are blood pH 7.10, pCO_2 35 mm Hg, and HCO_3 10 mEq/L. Using clues 1 and 2 would still support a single disorder (metabolic acidosis).

However, when the Winter's Formula is applied, we see that the predicted pCO_2 in a compensated simple metabolic acidosis should be $(1.5 \times 10) + 8 = 23$ mm Hg, which diverges from the measured value of 35. This patient has a higher than expected pCO_2 and thus a combined metabolic and respiratory acidosis. This double disorder results in a very acidemic pH.

Each of the single acid base disorders has a compensation formula similar to Winter's for metabolic acidosis. Using them in routine acid base analysis (or referring to a nomogram) allows better diagnosis of mixed acid-base disorders.

9 Pulmonology

Learning Objectives

- ❑ Interpret results of pulmonary function testing and chest radiography
- ❑ Diagnose disturbances of gas exchange
- ❑ Describe the presentation and management of obstructive lung disease, atelectasis, interstitial lung disease, and acute respiratory distress syndrome
- ❑ Outline the presentation, diagnosis, and management of sleep apnea
- ❑ List the types of lung cancer and their epidemiologic associations and prognosis
- ❑ Present risk factors, diagnosis, and treatment plan for pulmonary thromboembolism

PULMONARY PHYSIOLOGY FOR THE CLINICIAN

The respiratory system is responsible for 2 things: obtain oxygen from the environment for the utilization of energy in the form of ATP, and eliminate carbon dioxide, the waste product of cellular respiration.

Obtaining oxygen for cellular respiration can be divided into 2 processes, which illustrate the clinically relevant physiology required in patient management:

- Exchange of oxygen between alveoli and blood in the pulmonary capillaries ("oxygen diffusion," which applies Fick's law of diffusion); relevant for the following:
  - Evaluating A-a gradient or the response to supplemental oxygen
  - Determining DLCO
- Transport of oxygen in blood ("oxygen delivery")

Do not confuse oxygen delivery with total oxygen content and oxygen diffusion.

Total Oxygen Content

Total oxygen content in the blood is the sum of 2 measurable components:

- Amount of oxygen carried in the blood attached to hemoglobin, in RBCs
- Amount of oxygen dissolved in the plasma

Note

- A problem with the diffusion of oxygen is called **hypoxia**.
- A problem with the delivery of oxygen is called **hypoxemia**.

Note

The dissolved O_2 value is negligible, therefore is not usually considered in the clinical evaluation of O_2 delivery.

The relationship between these two forms is represented in an oxygen-hemoglobin dissociation curve. The proportion of hemoglobin bound to oxygen (saturated) is seen on the *y* axis, and the oxygen tension (dissolved oxygen) is seen on the *x* axis.

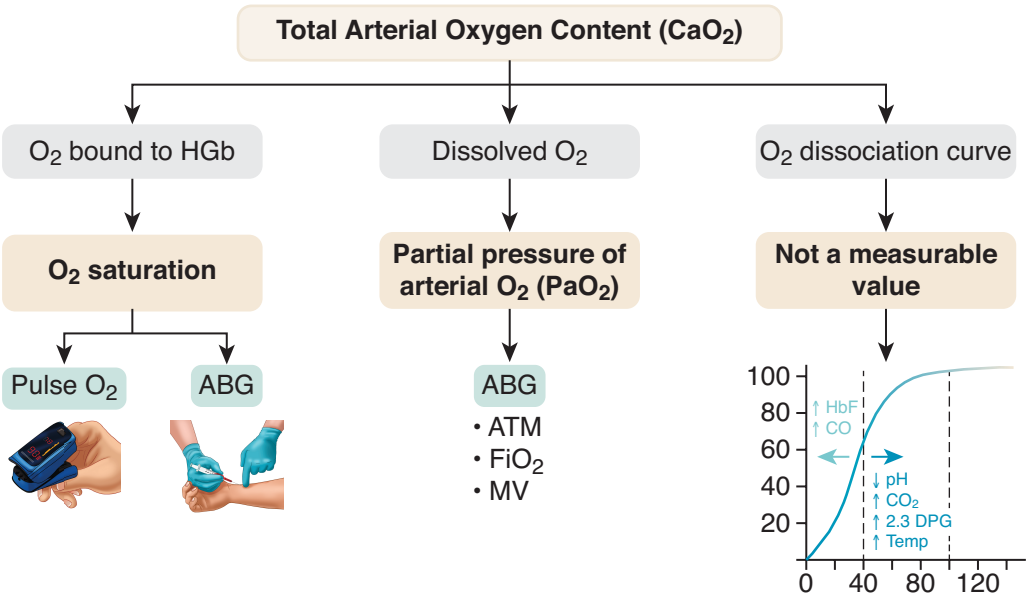


Figure 9-1. Total Arterial Oxygen Content

Table 9-1. Clinical Application of Oxygen Dissociation Curve

	PO2	Hb Concentraion	O2 per g Hb	O2 Content
Anemia	Normal	Decreased	Normal	Decreased
Polycythemia	Normal	Increased	Normal	Increased
CO poisoning (acute)	Normal	Normal	Decreased	Decreased

Note

For the exam, there is no need to memorize the oxygen delivery equations.

Oxygen Delivery

Oxygen delivery (DO_2) is the volume of oxygen that the tissues are receiving. CaO_2 is the amount of oxygen within the arterial blood. The following equations are used:

- $\mathbf{CaO_2 = (1.34 \times Hgb \times SaO_2) + (0.003 \times PaO_2)}$
- $\mathbf{DO_2 = CO \times CaO_2}$ (or $CO \times [(1.34 \times Hb \times HbSat) + (0.0031 \times PaO_2)]$

where Hgb is hemoglobin level, and SaO_2 is hemoglobin saturation.

Therefore, the oxygen received by the tissues relies on 2 main factors: **CO** (HR × SV) and **hemoglobin level.**

Alveolar-arterial (A-a) Gradient

The alveolar-arterial (A-a) gradient (the difference between A-aO_2) indicates the functionality of the alveolar-capillary unit. It increases physiologically with advancing age and pathologically with diseases of the lung.

Normal (healthy) A-aO_2 gradient is **5–15 mm Hg**. With hypoxia, that number is elevated, except when caused by hypoventilation or elevated altitude.

In order to determine the age-appropriate A-aO_2 gradient, use **A-aO_2 gradient ≤ (age/4) + 4**.

- First, calculate the PAO_2
  - PAO_2 = **[(Pb – PH_2O) × FiO_2] – [$PaCO_2$/0.8]**
  - Under normal conditions (at sea level): PAO_2 = [(760 – 47) × 0.209] – [$PaCO_2$/0.8]
  - PAO_2 = **150 – 1.25 ($PaCO_2$)**
- Next, calculate the alveolar-arterial gradient
  - PAO_2 – PaO_2 = **[150 – (1.25 × $PaCO_2$) – PaO_2]**

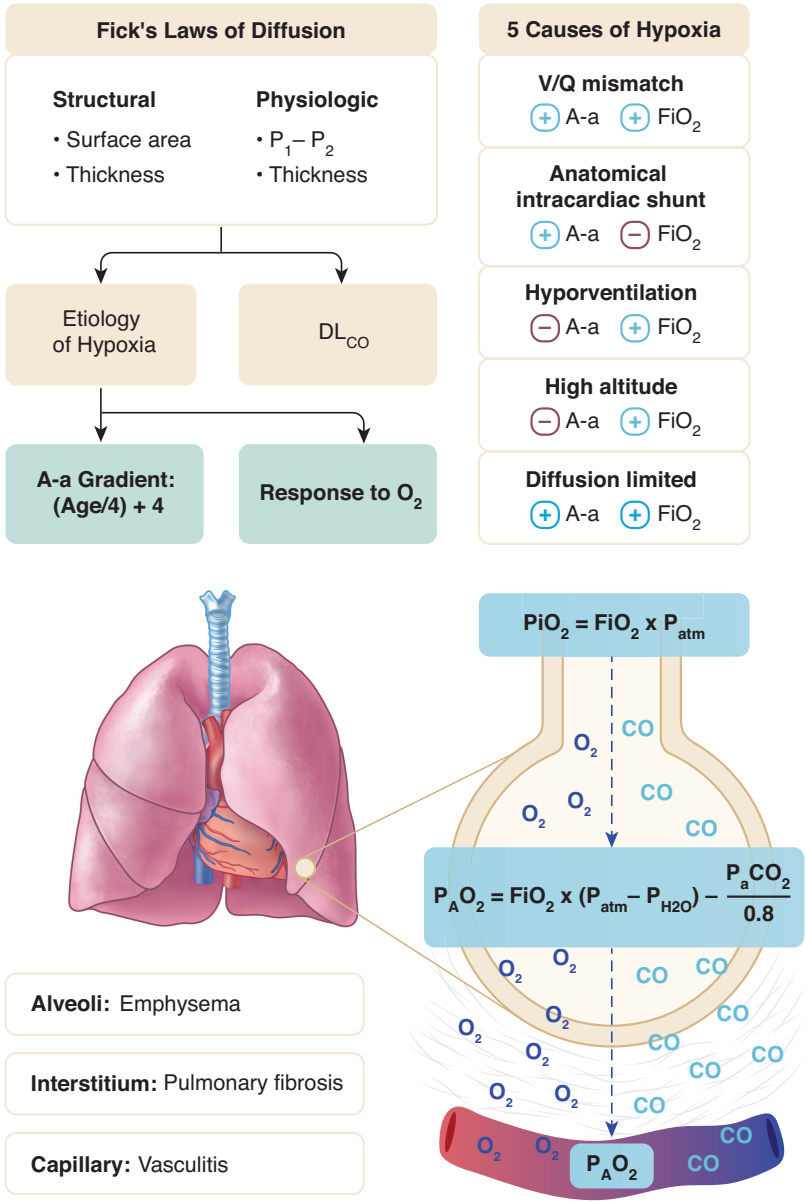


Figure 9-2. Clinical Physiology of the A-a Gradient

PAO_2 is partial pressure of the air within the alveoli (relatively constant among subjects), while PaO_2 is partial pressure of oxygen within the bloodstream, and usually obtained through the ABG (subject to variation based upon lung problems).

Hypoxia

Hypoxia is insufficient oxygen content in the tissues, caused by a pathological condition or a temporary variation in arterial oxygen concentrations (e.g., when exercising). To determine the etiology, one must determine if the patient's A-aO_2 gradient is normal or widened, as well as the response to supplemental O_2.

The causes of hypoxia are classified into categories.

- **Ventilation/perfusion (V/Q) mismatch** (**most common cause** of hypoxia in chronic lung disease)
  - Seen with alveolar disease (e.g., pneumonia), pulmonary vascular disease (e.g., PE), and atelectasis
  - Responds to O_2 supplementation
- **Right-to-left (R-to-L) anatomical intracardiac shunting**
  - Seen with intra-cardiac defects where deoxygenated blood is shunted from right to left
  - Does not fully respond to O_2 supplementation
- **Hypoventilation**
  - Seen with neuromuscular disease (e.g., ALS), CNS disorders or drug toxicity (e.g., opioids, barbiturates)
  - Usually associated with a high $PaCO_2$ with normal A-aO_2 gradient
  - Responds well to O_2 supplementation
- **Diffusion-limited ventilation**
  - Seen with pathologies affecting the alveolar-blood interface
  - Widening of A-a gradient
  - Responds to O_2
  - Supplementation
- **High altitude**
  - Low FiO_2– results in a reduced PAO_2
  - Normal A-aO_2 gradient
  - Responds to O_2 supplementation

POSITIVE PRESSURE VENTILATION

Positive-pressure ventilation is an artificial way to help inflate the alveoli in preparation for effective gas exchange and maintenance of patency. A ventilation device replaces the normal mechanisms and restores the functional surface area of the alveoli, leading to an effective gas exchange.

Positive-pressure ventilation is helpful for hypoxia that is not resolved by oxygen administration or for serving as a bridge while resolving the underlying problem. It is used frequently in the ICU. There are 2 classifications, both of which can cause a decrease in systemic venous return.

Noninvasive Ventilation

Noninvasive ventilation (NIV) ventilation with the use of a mask. It is less invasive and at times safer.

- **Continuous positive airway pressure** (CPAP) is used to create a pneumatic splint of the airways (keeping them continuously open, preventing collapse) through a constant air pressure (= 10 cm H2O)
  - Frequently used to manage OSA
  - Not commonly used for inpatient management of acute respiratory failure
- **Bi-level positive airway pressure** (BiPAP) applies to different pressures during the phases of breathing (e.g., BiPAP 10/5 cm H2O): a larger pressure is applied during inspiration and a smaller pressure during expiration which is equivalent to PEEP; this helps ventilate the patient and blow off CO_2.
  - Frequently used for acute/chronic respiratory failure, OSA, and obesity hypoventilation syndrome

Invasive Ventilation

Invasive ventilation is mechanical ventilation with endotracheal intubation or tracheostomy.

- Used during acute respiratory failure with the additional benefit of protecting the airway
- Preset with tidal volume (volume-controlled) or pressure range (pressure-controlled)
- Patients are started on 100% FiO_2 and ventilation is titrated based on oxygen saturation and ABG
- **Positive end-expiratory pressure** (PEEP) is a ventilator setting to prevent alveolar collapse; defines pressure at the end of expiration in alveoli; usual starting point is 5 cm H2O (>5 cm H2O ie, with ARDS to offset low tidal volumes which induce atelectasis)
- Watch for a drop in the systemic venous return to the right side of the heart (useful in treating CHF)

Note

Modern mechanical ventilation is referred to as **assist-controlled**, meaning the patient only has to trigger the ventilation to receive a tidal volume. Triggering is based on the generation of negative pressure or the flow by the patient. With this new technology, patients can breathe beyond the respiratory rate preset on the ventilator.

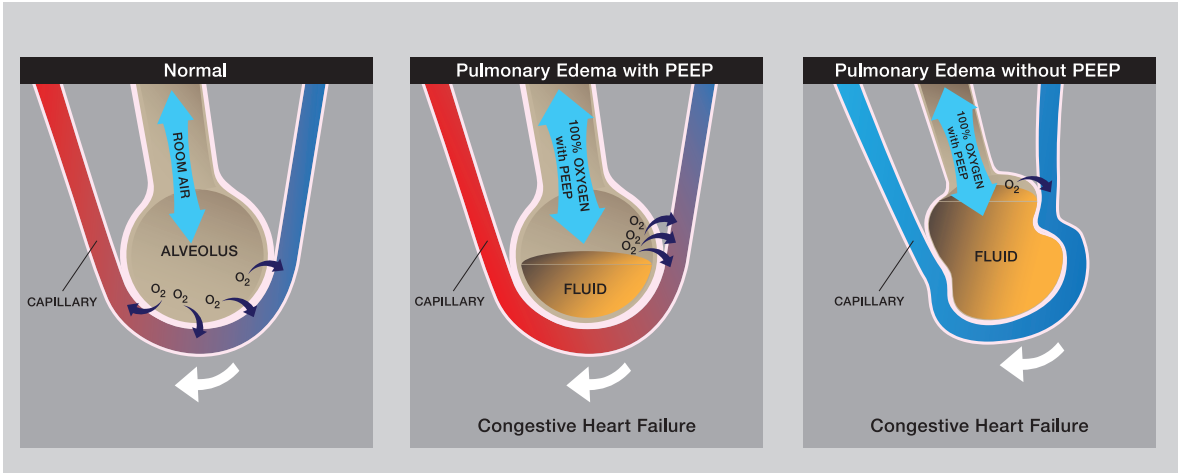


Figure 9-3. Effect of PEEP

TESTS FOR PULMONARY DISEASE

Diagnostic tests in pulmonology are used to identify the general condition, and then to investigate the source of the condition.

Clinical Pearl

Perform PFTs in all patients before they undergo lung resection surgery.

Pulmonary Function Tests

PFTs are non-invasive tests used to identify restrictive vs. obstructive disease, to assess disease severity (preop evaluation and overall prognosis), and to evaluate post-treatment lung function. The basic tests are spirometry, static lung volumes, and alveolar diffusing capacity of a gas.

- **Spirometry** (most common, can be done bedside/in office)
  - Determines most lung volumes and capacities, as well as expiratory flows and bronchodilator response (asthma evaluation)
  - Measures airflow/air movement by expiratory flow rate
  - When performing spirometry, a flow volume loop is obtained
  - Abnormal is generally **<70% of predicted** in any lung volume or flow rate
- **Static lung volume**
  - Volume measured is residual volume (RV), done in order to calculate total lung capacity (TLC) (defining value for restrictive disease)
  - **TLC = RV + VC or VC = TLC – RV**, where TLC is volume of gas in the lungs after maximal inspiration, RV is volume of gas remaining in the lungs after forced maximal expiration (unused space), and VC is volume of gas exhaled with maximal forced expiration
- **Alveolar membrane permeability** (DLCO) measures the alveolar membrane permeability
  - Determines how well (a) oxygen passes from alveolar space of the lungs into the blood, and (b) lungs are able to perform gas exchange
  - Single-breath DLCO test requires patient to inhale CO gas consisting of helium, CO, and room air
  - Diffusing capacity is reduced in following conditions:
    - When alveolar walls are destroyed and pulmonary capillaries are obliterated by emphysema
    - When alveolar-capillary membrane is thickened by edema, consolidation, or fibrosis (as in interstitial lung disease)

Clinical Correlate

- PFTs with an **obstructive pattern + decreased DLCO**: think emphysema
- PFTs with a **restrictive pattern + decreased DLCO**: think interstitial lung disease (intrapulmonary restriction) or mild left heart failure
- PFTs with **elevated DLCO**: think alveolar hemorrhage, polycythemia, and left-to-right intracardiac shunting (all secondary to the increased blood flow through the pulmonary capillaries or increased hemoglobin available at the level of the pulmonary capillaries)

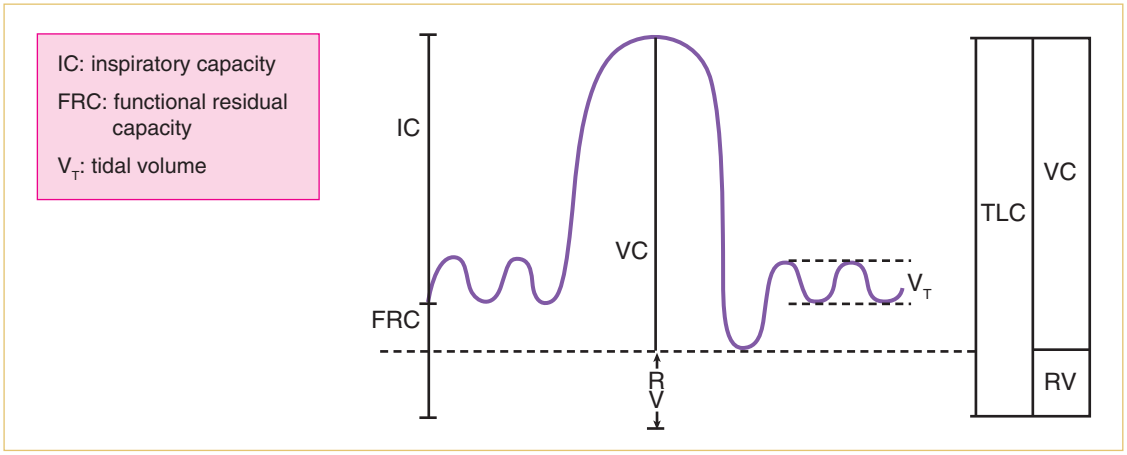


Figure 9-4. Determination of Lung Volumes

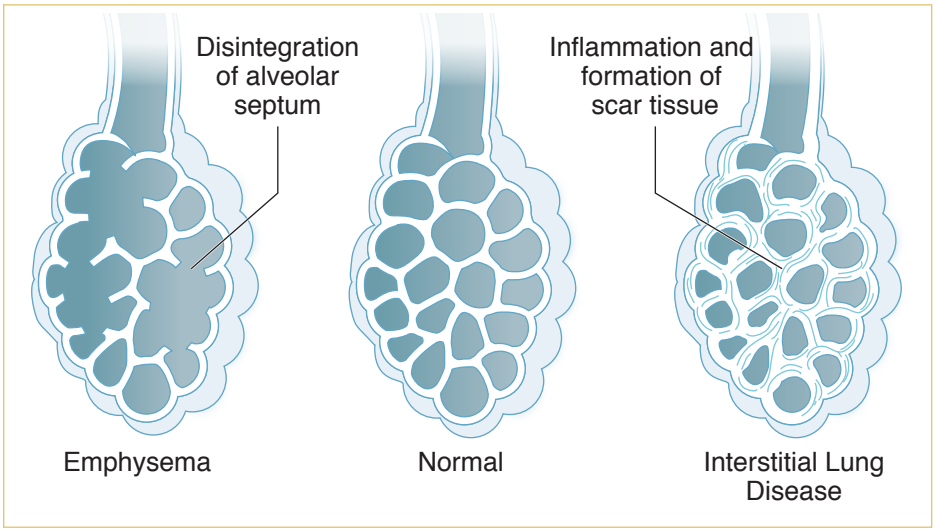


Figure 9-5. Alveolar Diffusing Capacity

Note

Common values obtained from spirometry include:

- **FEV1**: forced expiratory volume in 1 second
- **FVC**: forced vital capacity

The **FEV1/FVC ratio** is the defining **value for obstructive disease**.

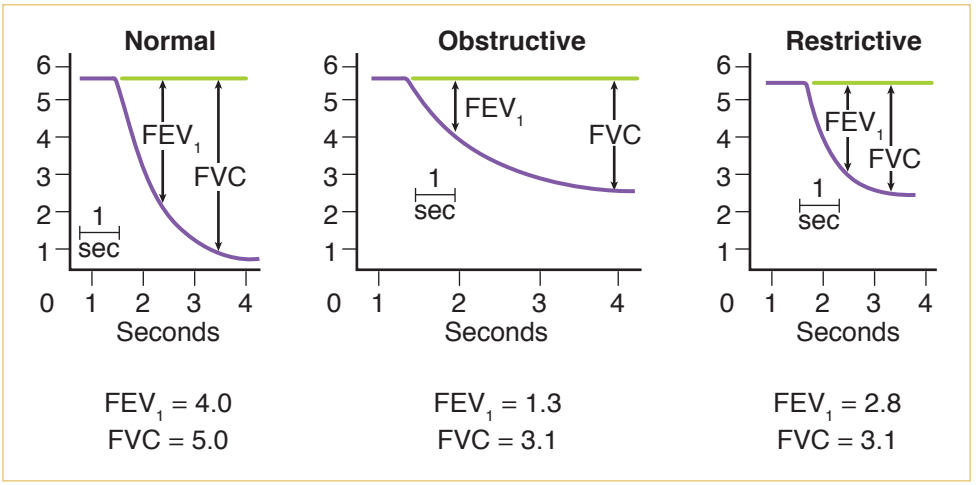


Figure 9-6. Forced Expiratory Volumes

Flow volume loop

Flow volume loop expresses airflow in lung disease, showing the relationship between flow rate and lung volume. It plots volume (*x*-axis) against flow rate (*y*-axis) during a maximally forced inspiration and expiration. The *x*-axis shows **volume** (lung volume increases to the left), and the *y*-axis shows **flow rate**.

Clinical Pearl

Some patients with asthma may have normal PFTs. In those cases, methacholine challenge will provoke an asthmatic crisis and allow a diagnosis of asthma to be made by PFTs. Thus, perform methacholine challenge only for patients with normal PFTs and in whom asthma is suspected.

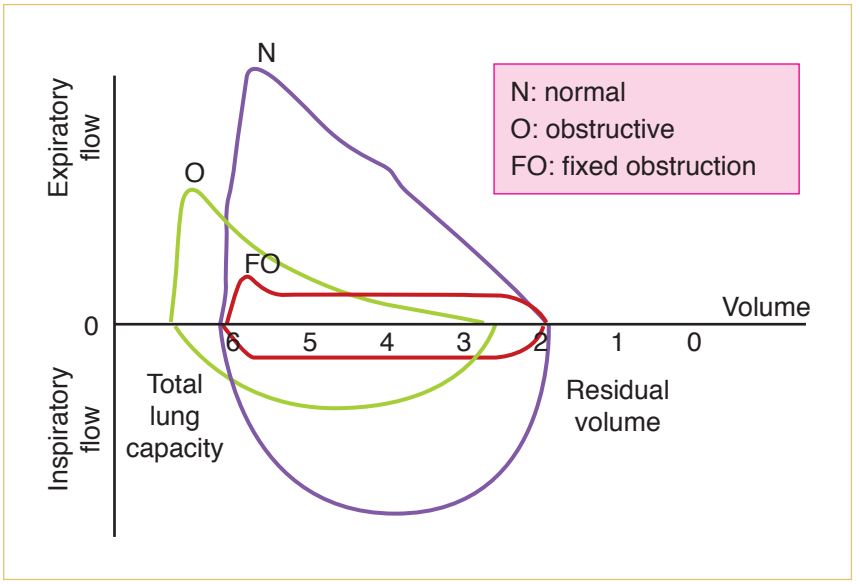


Figure 9-7. Flow Volume Loops

The shape of the loop can characterize the type and distribution of airway obstruction.

- **Restrictive lung disease** alters the size of the loop (a shift to the right of the *x*-axis), which is related to a reduction in lung volumes.
- **Obstructive lung disease** alters the shape of the loop by causing a reduction of airflow on the *y*-axis during expiration.
- **Fixed airway-obstruction** (tracheal stenosis after prolonged intubation) flattens the flow volume loop on the top and bottom.

With dynamic extra-thoracic upper airway obstruction, there are 2 main types: obstruction that occurs mostly with inspiration (ex bilateral vocal cord paralysis), and obstruction that occurs mostly with expiration, where there is a flattening of the expiratory part of the loop likely due to damage of the tracheal cartilage (ex tracheomalacia).

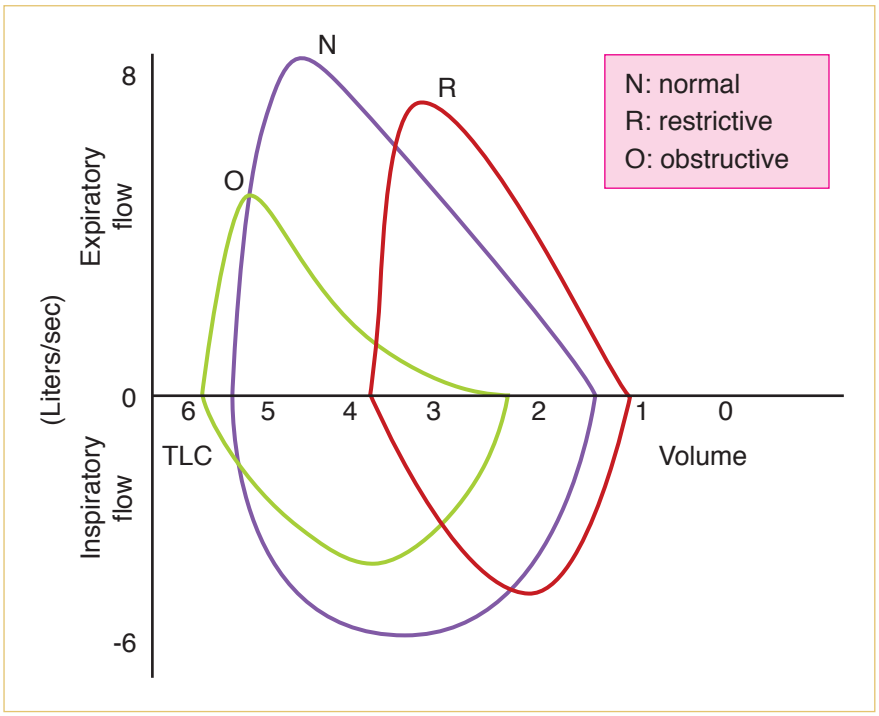


Figure 9-8. Flow Volume Loops

Clinical Pearl

FEO may occur in the setting of a tracheal tumor or foreign object aspiration or tracheal stenosis after prolonged intubation.

Methacholine challenge test

The methacholine challenge test evaluates cough-variant asthma or exercise-induced bronchoconstriction in the presence of normal PFTs and no bronchodilator response (a common scenario with asthmatics).

- Patient inhales methacholine and bronchoprovocation is evaluated
- The results of PFTs performed before and after the inhalation (e.g., spirometry) are used to quantitate the response.
- A **decrease ≥20% from baseline FEV1** is considered **positive**

Imaging

Noninvasive Testing

Various non-invasive technologies allow physicians to observe a specific pathology: chest x-ray, chest CT, PET scan, and lung biopsy.

Note

In pregnancy, U/S is used instead of CT.

- **Chest x-ray** (**most common**)
  - Usually the first diagnostic test in the evaluation of pulmonary complaints/ respiratory symptoms
  - May also show initial evidence of pulmonary disease in the absence of symptoms, e.g., pulmonary nodule found incidentally on chest x-ray
  - Not a confirmatory test for a diagnosis such as pleural effusion, interstitial lung disease, or nodule
- **Chest CT** (more detailed but there is a negligible risk of cancer)
  - Used to assess the mediastinum, pleura, and parenchyma
  - Cost-effective
  - Can be performed in the presence of metallic equipment (e.g., pacemaker) and is less sensitive to patient's movement
  - CT pulmonary angiography uses a rapid-timed infusion of IV contrast dye to enhance the imaging of the pulmonary vasculature during the bolus phase to assess for PE
  - Low-dose CT is used as a screening tool for lung cancer (USPTF guidelines), while high-resolution CT uses smaller slices and no contrast to assess for interstitial lung disease
- **PET scan** (functional imaging) provides a metabolic profile of lesions. It is usually compared with anatomical imaging (CT) to localize the metabolically active tissues.
  - Used to differentiate some benign lesions (e.g., scars) from pulmonary lesions that are malignant, infectious, or inflammatory
  - Cannot differentiate between malignant, infectious, and inflammatory lesions
  - Good for metabolically active tissue
  - Excellent at detecting disease in its early stages
  - Intensity of the FDG uptake can guide clinical decision-making (paired with CT, can localize FDG avidity by metabolically active cells)

Note

BAL differs from bronchial washings in which secretions are aspirated from multiple parts of the pulmonary tree and not from a specific sub-segment.

Invasive Testing

- **Lung biopsy** allows microscopic examination and staining of a piece of the lung that may contain pathology.
  - Can be performed percutaneously (CT-guided), via bronchoscopy, or via surgery (open or VATS)
  - Indications include a peripheral pulmonary nodule where traditional bronchoscopy may not be able to reach the intended lesion
  - CT-guided biopsy (percutaneous transthoracic needle biopsy) allows real-time imaging via CT in conjunction with percutaneous needle biopsy to remove samples of lung tissue; has fewer complications than other procedures but caution in those with emphysema due to the increased risk of pneumothorax

Note

Because of its invasive nature, **mediastinoscopy** is now being replaced with endobronchial U/S.

- **Bronchoscopy** is an endoscopic technique used to visualize the inside of the airways and to perform procedures and biopsies. A device is inserted through the mouth, nose, or tracheostomy site along the walls of the airways.
  - **Flexible** bronchoscopy (**most common**) is helpful for the following:
    - BAL (collection of bronchoalveolar washings in the sub-segmental bronchi after infusion of saline into the alveoli); indications include non-resolving pneumonia, diffuse lung infiltrates (especially in immunocompromised patients), diffuse non-infectious pulmonary disease, and suspected alveolar hemorrhage.
    - Bronchial brushing to sample the lung (used most often in infection and malignancy evaluation)
    - Endobronchial biopsy
    - TBB (used to obtain a piece of lung tissue); associated with less morbidity and mortality than open biopsy. Indications are to diagnose lung nodules, pulmonary infections in immunocompromised patients, and acute allograft rejections in lung transplant patients.
    - FNA of a mediastinal lymph node
    - Endoscopic bronchial U/S (U/S in conjunction with a bronchoscope) to visualize the airway wall and surrounding structures; indications include staging of lung cancer, mediastinal lymphadenopathy, intrapulmonary nodules, and endobronchial lesions
  - **Rigid** bronchoscopy (usually performed in the OR) is helpful for foreign body removal and advanced airway management; complications include injury to lips, teeth and tongue, and pneumothorax (rare)
- **Open lung biopsy**: under general anesthesia, excision of lung tissue/lung lobe as needed; performed only after minimally invasive procedures have failed to yield a significant diagnosis; requires hospital stay and has complications
- **VATS**: minimally invasive lung biopsy similar to laparoscopy; indications are similar to those for lung biopsy, plus pulmonary decortication, pleurodesis, and lung/pleural biopsy

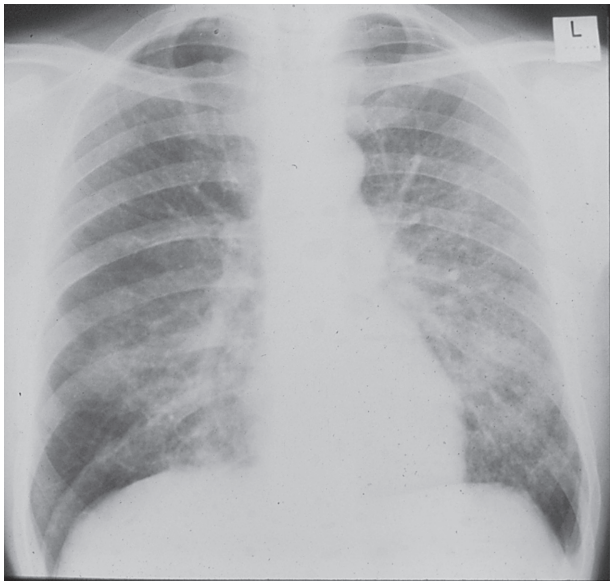


Figure 9-9. Bilateral Interstitial Infiltrates on Chest X-ray

Clinical Correlate

- PET scan is good for metabolically active tissue because this type of tissue needs glucose, and the tracer of a PET scan mimics glucose (hence 18F-fluorodeoxyglucose). The tracer gets taken up if the tissue is metabolically active.
- This explains why PET scan is used in cancer evaluation and staging.

To describe a chest x-ray, use ABCDE:

- **Airway**
  - Is the trachea shifted?
  - Look at the carina and the main stem bronchus.
- **Bone**
  - Fractures
  - Compression fracture of the spine (lateral view)
- **Cardiac and mediastinum silhouette**
  - Cardiomegaly, chamber enlargement
- **Diaphragm**
  - Look under it, through it, and above it
  - Where is the stomach bubble?
- **Everything else**
  - Lines and tubes
  - Lungs (one at a time)
  - Nodules
  - Markings: vascular (more central) and interstitial (more peripheral)

OBSTRUCTIVE LUNG DISEASE

The obstructive disease process leads to expiratory airflow limitation in patients. It may be reversible (asthma) or irreversible (COPD).

Asthma

A 26-year-old woman with a history of asthma presents to the ED with 3 days of progressive wheezing and shortness of breath after an upper respiratory tract infection. She is taking inhaled albuterol and an over-the-counter medication for her cold symptoms. Her respiratory rate is 28/min and pulse 110/min; she is afebrile. Her right nasal turbinate is edematous and erythematous. There is evidence of wheezing throughout both lungs, but no crackles are noted. Supplemental oxygen by nasal cannula is administered.

Asthma is characterized by inflammatory hyperreactivity of the airways (bronchial hyperreactivity) to various stimuli, resulting in reversible airway obstruction. Bronchial obstruction occurs as a result of mucosal inflammation, bronchial musculature constriction, and excessive secretion of viscous mucus plugs. The bronchial hyperreactivity occurs in an episodic pattern secondary to "triggers," with interspersed normal airway tone.

Asthma can occur at any age but is usually seen in young people; about half outgrow their asthma by adulthood.

There are 2 types of asthma. Many patients have features of both types.

- **Extrinsic (allergic, atopic)** asthma (**very common**)
  - Results from sensitization
  - Total serum IgE concentration is elevated
  - Precipitated by allergens; other symptoms include allergic rhinitis, urticaria, and eczema
  - Prognosis is good; many new biological agents target moderate-to-severe persistent extrinsic allergic asthma
- **Intrinsic or idiosyncratic** asthma (small number of cases)
  - Bronchial reaction
  - Secondary to nonimmunologic stimuli, such as infection, drugs, irritating inhalants, cold air, exercise, or emotional upset

Asthma is a narrowing of the large and small airways caused by hypertrophy and spasm of bronchial smooth muscle, edema, inflammation of the bronchial mucosa, and mucus production.

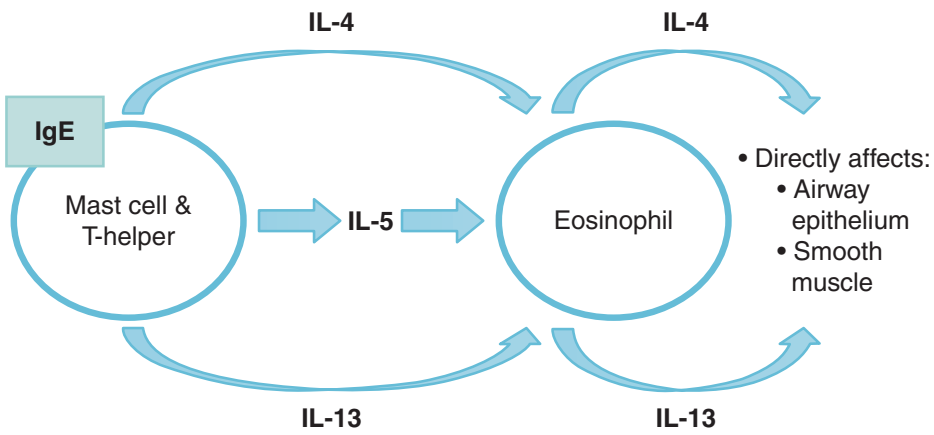


Figure 9-10. Pathway of Allergic Asthma

Clinical Presentation.

- Recurrent episodes of wheezing and chest tightness at night or early morning
- Slight tachypnea (increased respiratory rate), tachycardia, prolonged expirations, and mild, diffuse wheezing (mild attacks)
- Use of accessory muscles of respiration, diminished breath sounds, loud wheezing, hyper-resonance and intercostal retraction (severe attacks)
- Nocturnal cough and exercise-induced bronchospasm (seen in variants of asthma)

Note

Samter's triad includes asthma, nasal polyposis (causing recurrent sinus disease), and sensitivity to aspirin and NSAIDs.

Clinical Correlate

Cells thought to play an important role in the inflammatory response are those in both the innate and adaptive immune systems:

- Macrophages
- Mast cells
- Lymphocytes
- Eosinophils
- Specific interleukins (mainly IL-5, IL-4, IL-13)

Diagnosis is based primarily on the history and physical examination. Spirometry and/or full PFTs show an obstructive pattern that typically reverses with bronchodilation. Spirometry using FEV1 is not the best indicator of severity without a good history and physical examination.

Note

Variants of asthma include asthma presenting primarily with nocturnal cough and exercise-induced asthma (commonly tested on the exam).

- PFTs may be normal without bronchial hyperreactivity; in that case, a provocative challenge with methacholine, exercise, or histamine will show decreased FEV1 or FVC >20%
- FEV1 or FVC must show 12% and/or 200 mL reversibility with use of beta-2 adrenergic agonist
- Chest x-ray findings are nonspecific in an asthma exacerbation. They may be helpful in ruling out acute infection as the cause of the exacerbation.
- **Acute asthma**: ABG abnormalities consistent with tachypnea (decreased arterial carbon dioxide tension ($PaCO_2$), increased pH, normal PaO_2 (may be low with significant airway obstruction)
- **Severe asthma or status asthmaticus**: decreased PaO_2, increased $PaCO_2$, decreased pH
  - In an acute setting, bicarbonate is not usually elevated, but it does elevate with chronic respiratory acidosis.
  - In an acute setting, normal $PaCO_2$ may indicate the beginning of respiratory muscle fatigue.

Table 9-2. Asthma Classification

Asthma exacerbation: SABA as needed (3 doses/IV x 1 hr), SpO_2 >92%, IV fluids, ipratropium bromide, systemic glucocorticoids (impending respiratory failure), $MgSO_4$ if severity constant even after 1 hr of bronchodilatory therapy				
How to Classify?				**Asthma Classification (age ≥12)**
	Intermittent	**Persistent**		
		Mild	**Moderate**	**Severe**
Symptoms	≤2x/wk	>2x/wk	Daily	Many times/day
Nighttime awakenings	≤2x/mo	3-4x/mo	>1x/wk	4-7x/wk
SABA use frequency	≤2x/wk	>2x/wk	Daily	Many times/day
Limitation of activities	None	Minor	Moderate	Major

Treatment. The foundation of treatment is bronchodilators, oxygen, steroids, and airway protection if unstable, and chronic outpatient therapy if stable.

Medical therapy is as follows:

- **Inhaled corticosteroids** (**mainstay of chronic asthma therapy in adults**) work by reducing airway inflammation
  - Review with patients the correct technique for inhaler use, including the use of spacers and mouth-rinsing to avoid oral candidiasis
  - Side effects include glaucoma, cataracts, diabetes, muscle weakness, and osteoporosis
- **Beta-adrenergic agonist inhalers** (used in acute and chronic asthma therapy) act on β_2-adrenergic receptors to cause smooth muscle relaxation (bronchodilation)
  - Inhaled (metered-dose inhalers [MDIs] are the preferred route because they allow maximal bronchodilation with minimal side effects)
  - Side effects include tremor and tachycardia (consider levalbuterol, especially if patient has Afib)
    - **Short-acting beta agonists (SABA)** (inhaled SABAs such as albuterol are the **mainstay of chronic asthma therapy**, usually used with inhaled corticosteroids)
      - All asthmatics should carry a SABA, to be used "as needed" for SOB or cough, up to 2 puffs every 4 hrs.
      - Use of SABA ≥ 3 days/wk indicates poor control of symptoms, and treatment should be intensified.
    - **Long-acting beta agonists (LABA)** (for moderate to severe persistent asthma, after initial therapy with SABA + inhaled corticosteroids, especially with a significant nocturnal component)
      - Not for use during acute exacerbation or for use alone (i.e., always use in conjunction with inhaled corticosteroids)
      - Inhaled LABAs, such as salmeterol and formoterol, have a sustained effect on bronchial smooth muscle relaxation
      - LABA monotherapy has numerous side effects and is associated with an increase in asthma-related deaths.
- **Anticholinergic drugs** (ipratropium bromide, tiotropium) act as antagonists to M3 receptors of smooth muscle in the airway
  - **Short-acting:** very effective for acute exacerbation of asthma in conjunction with beta 2 agonist
  - **Long-acting**: if symptomatic even after ICS/LABA therapy, add a LAMA
- **Leukotriene modifiers**
  - **Zileuton**: inhibits 5-lipoxygenase, the enzyme involved in leukotriene production (LTC4, LTD4, LTE4)
  - **Montelukast** and **zafirlukast**: cysteinyl leukotriene-1 (CysLT1) antagonists
  - Approved for severe asthma resistant to maximum doses of inhaled corticosteroids and as a last resort before using chronic systemic steroids
- **MAST cell stabilizers** (cromolyn sodium, nedocromil)
  - Inhibit release of contents of mast cells (mast cell degranulation); used for chronic asthma, not immediate asthma relief
  - Less effective than inhaled corticosteroids at preventing asthma exacerbation and reducing inflammation in adults and children

Note

With asthma, caution with aspirin/NSAIDs (due to possible Samter's Triad) and non-selective beta-adrenergic antagonists. Infections can trigger both intrinsic and extrinsic asthma (classic infections are RSV in children and rhinoviruses in adults).

Note

Neither short-acting nor long-acting beta 2 agonists address the inflammatory component of asthma.

- **Biologics** (reserved for moderate to severe persistent allergic asthma that is refractory to traditional inhalers and patient is oral-steroid-dependent)
  - **IgE antibody**: omalizumab (indicated for elevated IgE in both children and adults); an injectable medication administered in a health care setting due to the risk of anaphylaxis (patient must carry an Epipen at all times); dosing is based on symptoms (not IgE level), usually every 3–4 weeks
  - **IL-5 inhibitors:** mepolizumab, benralizumab, and reslizumab (indicated for elevated eosinophils noted on patient's CBC); work as antibodies that bind and inactivate interleukin-5, which leads to the activation of eosinophils
  - **IL-4 and IL-13 inhibitors**: dupilumab, an at-home injectable medication indicated for elevated eosinophils on CBC and when patient cannot taper off steroids

Severe persistent allergic asthma refractory to inhalers is treated with monoclonal antibody drugs.

Note

If a patient has contraindications to LABAs, LAMAs can be used instead.

Note

Methylxanthines (theophylline, aminophylline) are seldom used in asthma and are usually the wrong answer on the exam.

Note

Bronchodilators do not address the inflammatory component of asthma.

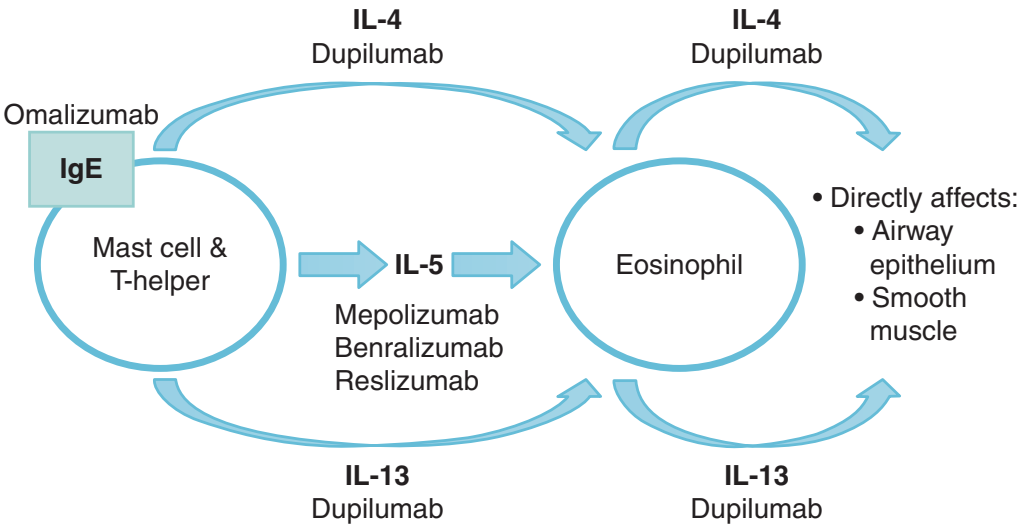


Figure 9-11. Mechanism of Action of Biologic Drugs Used in Persistent Allergic Asthma

Avoid corticosteroids in the management of chronic asthma when possible. Remember the side effects with CUSHINGOID.

- **C**: cataracts/candidiasis (oral, through improper use of ICS)
- **U**: ulcers
- **S**: striae, skin thinning
- **H**: hypertension, hirsutism
- **I**: immunosuppression, infections
- **N**: necrosis of femoral heads
- **G**: glucose elevation
- **O**: osteoporosis, obesity
- **I**: impaired wound healing
- **D**: depression/mood changes

During the exam, you must distinguish whether the question is asking about acute asthma management or chronic asthma. Some general guidelines are as follows:

- Management of **acute exacerbations**
  - Inhaled (preferably nebulized) beta 2 agonist (e.g., albuterol) and anticholinergics (e.g., ipratropium)
  - Oxygen as needed to maintain SpO_2 ≥92%
  - IV fluids (normal saline) as needed for hypotension
  - Systemic glucocorticoids (e.g., methylprednisolone, dexamethasone); route of administration depends upon clinical severity
  - If no response to initial treatment, use a one-time infusion of magnesium sulfate (modest evidence of benefit and low likelihood of harm)
  - Transfer all patients to an appropriate care setting based upon clinical presentation, with a low threshold for ICU monitoring
- Management of **chronic asthma**
  - Non-pharmacological/lifestyle measures
  - Avoid triggers (crucial but can be difficult to identify triggers)
  - Remove (or minimize contact with) environmental irritants and allergens, such as pets and dust
  - Involve patients by using an action plan for self-triage: green zone when asthma under control; yellow zone when asthma not well-controlled; and red zone when asthma out of control and needs emergent medical attention

There are 3 pathologies associated with asthma.

- **EGPA** (eosinophilic granulomatosis with polyangiitis)
  - Common in men, age 20–40
  - Small-and-medium vessel vasculitis with rhinosinusitis, asthma (90% of EGPA patients have asthma), and eosinophilia; peripheral neuropathy (mononeuritis multiplex); GI/respiratory tract involvement
  - Labs show elevated IgE, p-ANCA positive (antibodies directed against myeloperoxidase)
  - Treatment: steroids, mepolizumab (newly approved IL-5 blocker)
- **CEP** (chronic eosinophilic pneumonia)
  - Common in women, age 30–40
  - Asthma (50% of cases)
  - Labs show peripheral blood eosinophilia (unlike acute eosinophilic pneumonia, where eosinophils can be normal) and elevated IgE
  - Treatment: steroids (use long taper, as relapse is common)
- **ABPA** (allergic bronchopulmonary aspergillosis)
  - Non-invasive allergic lung reaction to a fungus (commonly *Aspergillus fumigatus*)
  - Rather than invading the lung tissue and destroying it, the fungus colonizes the mucus in the airways of patients with asthma or CF (both conditions have increased mucus) and causes allergic inflammation in the lung
  - Diagnosed with major and minor criteria
  - Bronchiectasis and scarring if extensive damage has occurred
  - Treatment: oral steroids; antifungals (steroid-sparing agents), omalizumab (for patients with elevated IgE and taking steroids)

Diagnostic Criteria for ABPA

- Predisposing conditions (**one must be present**): asthma or CF
- Major criteria (**both must be present**): *aspergillus* skin test positivity or detectable IgE levels against *A. fumigatus and elevated* total serum IgE concentration (typically >1,000 IU/mL, but <1,000 IU/mL may be acceptable if patient meets all other criteria)
- Minor criteria (**≥2 must be present**)
  - Precipitating serum antibodies to *A. fumigatus*
  - Radiographic pulmonary opacities consistent with ABPA
  - Total eosinophils >500 cells/microL in glucocorticoid-naïve patients (may be historical)

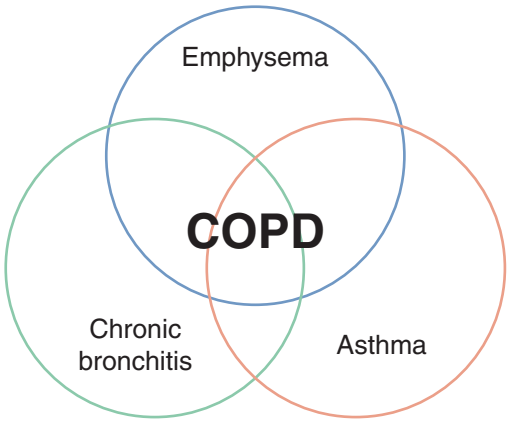
Chronic Obstructive Pulmonary Disease

A 67-year-old woman with COPD is evaluated for dyspnea that occurred the prior day. She denies fever and chills but has noted productive cough. Her medications include ipratropium MDI. Her respiratory rate is 32/min and pulse 106/min; she is afebrile. She looks cachectic and is breathing fast. You note an increased anteroposterior diameter, distant heart sounds, and expiratory wheezing.

Chronic obstructive pulmonary disease (COPD), a common condition with high morbidity and mortality, is an umbrella term to describe emphysema (pink-puffer), an anatomic/histologic diagnosis, chronic bronchitis (blue bloater), a clinical diagnosis (cough, and sputum >3 months in 2 successive years), asthma and COPD overlap syndrome (ACOS), and bronchiectasis.

COPD should be considered in anyone with dyspnea, chronic cough with sputum production, and/or a history of exposure to risk factors for the disease. There are 2 main etiologies:

- **Smoking** (80–90% of cases)
  - COPD symptoms usually begin after 20 pack-years of tobacco exposure; 10–15% of smokers develop COPD
  - Number of pack-years of smoking often correlates to reduction of FEV1
- **Non-smoking** (10–20% of cases)
  - Air pollution, airway infections, and allergies can lead to bronchitis
  - Alpha 1-antitrypsin deficiency, a rare hereditary autosomal recessive disease, can cause emphysema and liver abnormalities



Note

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) has developed a system for categorizing COPD severity according to frequency of symptoms, severity, and risk of exacerbations.

You will not need to memorize these categorizations for the exam.

Note

COPD is the only cause of death among the top 5 in the United States that is increasing in frequency. It is a leading cause of death worldwide.

After long-term exposure to cigarette smoke, inflammatory cells are recruited in the lung.

- The inflammatory cells in turn secrete proteinases, which may lead to destruction of the acinus (lung structures distal to the terminal bronchiole, including alveolar ducts, alveolar sacs, and alveoli).
- Alpha-1 antitrypsin can combat these proteinases, explaining the early emphysema in patients with alpha-1 antitrypsin deficiency.
- Over time, decreased elastic recoil (mainly with emphysema) and increased airway resistance (mainly with chronic bronchitis) occur.
- The chronic inflammation causes structural changes, small airways narrowing, and destruction of lung parenchyma.

Symptoms of COPD include cough, sputum production, and dyspnea on exertion (all common). Daily sputum production may precede the dyspnea by many years.

Diagnosis requires spirometry with post-bronchodilator FEV1/FVC <0.70.

- Chest x-ray is essential in evaluating SOB and other pulmonary symptoms but is neither sensitive nor specific for diagnosing COPD and does not reliably reflect the severity of the disease.
- Classic findings of emphysema include hyperinflation; flattening of diaphragm (lateral view); and widening of retrosternal airspace (lateral view) on PA and lateral chest x-ray).

Treatment begins with education about smoking cessation and COPD, and then as follows:

- **Acute exacerbation**
  - Systemic glucocorticoids: oral prednisone when urgent admission not required
  - Inhaled short-acting bronchodilator therapy (alternatives include a short-acting anticholinergic agent, e.g., ipratropium alone or in combination with a SABA)
  - Antibiotics if bacterial bronchitis or pneumonia is suspected
  - Supplemental oxygen titrated to target 90–92% SpO_2 when there is hypoxia due to an exacerbation of COPD
  - Noninvasive ventilation (NIV) (e.g., BiPAP); if NIV contraindicated, consider invasive mechanical ventilation
- **Chronic management** (pulmonary rehabilitation improves symptoms, exercise capacity, and quality of life)
  - SABA, SAMA, or both to relieve intermittent increases in dyspnea
  - If symptoms persist, LABA, LAMA, or both
  - If symptoms still persist, inhaled corticosteroids to decrease exacerbations and slow progression of respiratory symptoms (but have little impact on lung function)
    - Start at same time as a LABA if there are signs of inflammation or asthmatic component to the COPD
    - Side effects include dysphonia, skin bruising (elderly patients), oral candidiasis (at higher doses), increased incidence of pneumonia and cataracts, and diminished bone density (at higher doses)

  - Long-term oxygen therapy for COPD patients with chronic hypoxemia (resting arterial oxygen tension (PaO_2) ≤55 mm Hg or pulse oxygen saturation (SpO_2) ≤88%)
  - Yearly influenza vaccine, pneumococcal polysaccharide vaccine, and conjugate pneumococcal vaccine (for those age >65)
  - Roflumilast: phosphodiesterase-4 inhibitor to prevent future exacerbations in severe COPD, particularly in those who experienced ≥1 exacerbation in the past year and have predominantly chronic bronchitis phenotype
  - Azithromycin to prevent future exacerbations and improve quality of life
    - Use caution, as a side effect of azithromycin is slightly increased risk in cardiovascular death
    - Risk is highest among those with a high baseline risk of cardiovascular disease

The main interventions that have been shown to decrease mortality in COPD are **home oxygen** and **smoking cessation**; however, consider lung volume reduction surgery and lung transplant in selected patients.

- Home oxygen therapy (goal is to maintain O_2 saturation >90%, especially at night when patients desaturate)
  - Use for patients with hypoxemia (PaO_2 <55 mm Hg or saturation <88%)
  - Use for patients with cor pulmonale (right-sided heart failure) when PaO_2 <59 mm Hg
  - Use intermittent oxygen for patients who desaturate with exercise
- Tobacco cessation: slows progression of COPD and slows decrease in FEV1
- Lung volume reduction surgery (proven to prolong survival only in patients with mainly upper-lobe emphysema and poor exercise capacity)
  - Removal of ruined areas of the lung in an attempt to reduce hyperventilation (reduction of dead space) and improve chest wall and diaphragm dynamics
  - Endobronchial valves are newly-approved, minimally-invasive, bronchoscopically implanted devices that permit exhalation and drainage of secretions but prevent air entry during inspiration
- Lung transplant (proven to prolong survival in patients with COPD)
  - Substantial improvement in exercise tolerance and quality of life
  - Transplant recipients are at risk for infection secondary to immunosuppression, toxic effects of immunosuppressant drugs, and acute and chronic rejection of the lung allograft
  - Single or double lung transplants are possible

Returning to our patient in the vignette, she is likely to have a decreased DLCO on her PFTs. Treatment of her acute exacerbation would be with systemic steroids, antibiotics, and bronchodilators, with O_2 as needed. Treatment when she goes home will include an ipratropium inhaler and home O_2 (if she has chronic hypoxemia). The severity of her disease should be assessed by measuring FEV1.

Bronchiectasis

A 17-year-old girl is admitted to the hospital with a right lower lobe pneumonia. She provides a history of recurrent pneumonias, some of which have kept her in the hospital for weeks, and of chronic productive cough that occurs every day. Her parents add that she has had "loose stools" since childhood. On examination she is found to be thin and in distress. There are diminished breath sounds on the right lower lobe with rhonchi.

Note

Bronchi means airways of the lung, and *ectasis* means an organ that is enlarged or dilated.

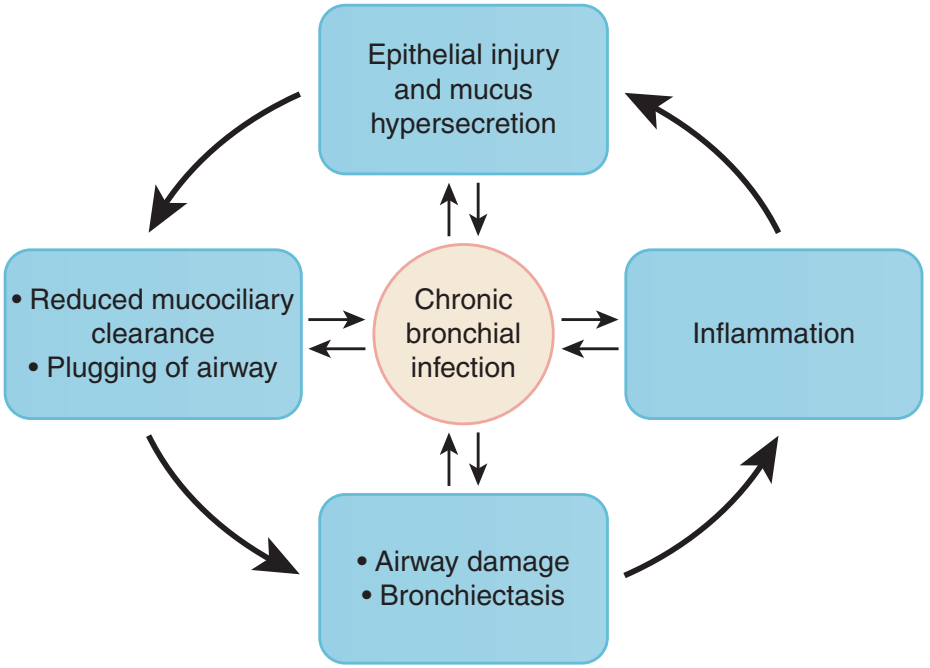
Clinical Correlate

Neutrophil elastase is known as one of the most destructive enzymes in the body.

Bronchiectasis means "dilated airways," meaning the permanent dilation of small- and medium-sized bronchi resulting from destruction of bronchial elastic and muscular elements with eventual fibrosis of the bronchi. The progressive airway destruction may be related to the unopposed activity of neutrophil elastase (usually balanced by α1-antitrypsin activity).

The cause of bronchiectasis is recurrent pulmonary infection. Immune deficiency can play a role. Clinical features include:

- Chronic cough
- Copious, viscid sputum production that is foul-smelling
- Airway dilation (honeycombing)
- Bronchial wall thickening (tram-tracks)
- Significant history of recurrent pneumonia that commonly involves gram-negative bacteria (especially *Pseudomonas species*)



The etiologies of bronchiectasis are CF and non-cystic fibrosis.

Cystic fibrosis bronchiectasis

Cystic fibrosis (CF) is a multisystem disorder caused by mutations of the CF transmembrane conductance regulator (CFTR) gene. A small number of patients present with CF in early adulthood. Pulmonary disease is the most common cause of morbidity and mortality.

- Symptoms include diffuse bronchiectasis; chronic productive cough (especially if there is a history of recurrent sinusitis, nasal polyps, and weight loss); infertility in men
- Symptoms are consistent with CF in ≥1 organ system PLUS evidence of CFTR dysfunction (elevated sweat chloride or evidence of disease-causing mutations in CFTR)
- Treatment: CFTR modulators (ivacaftor, tezacaftor-ivacaftor); airway clearance therapies (inhaled airway clearance agents [dornase alfa, hypertonic saline], chest physiotherapy, exercise); bronchodilators (inhaled β2 agonists, anticholinergics); anti-inflammatory agents (azithromycin, ibuprofen); lung transplant if no response
- Prevention of infection: vaccination (influenza and Pneumococcal), palivizumab (humanized monoclonal antibody against RSV), and other general precautions

Non-cystic fibrosis bronchiectasis

Non-CF is a focal bronchiectasis caused by infection, impairment of drainage, airway obstruction, and a possible defect in host immune response. Causes include:

- Local infection (recurrent gram-negative infection, TB, other mycobacterial infections, fungal infections, *Nocardia*); lung abscess; or pneumonia
- Chronic inflammatory disease, e.g., Sjogren syndrome, SLE, rheumatoid arthritis
- Inadequate clearance of secretions: mucous plugging (primary ciliary dyskinesia, Young syndrome); anatomic bronchial defects; bronchial obstruction: intraluminal obstructing lesion from a cancer or mass; immunosuppression
- Genetic: alpha-1 antitrypsin deficiency (current guidelines recommend testing in patients with bronchiectasis and no other evident etiology)

Diagnosis.

- Chest x-ray: early findings may be normal, while advanced cases may show 1- to 2-cm cysts and thickened airways (tram-tracking, i.e., appear like rings on cross-section); radiologic classifications of bronchiectasis include:
  - Cylindrical
  - Varicose
  - Cystic (or saccular)
- Chest CT to confirm; may show signet-ring appearance, tram-track lines and honeycombing
- A normal sweat chloride result is usually sufficient to rule out CF.

Note

In Young syndrome, patients have no evidence of CF but they do have bronchiectasis, sinusitis, and obstructive azoospermia. Possible causes include childhood exposure to mercury or misidentification of primary ciliary dysfunction.

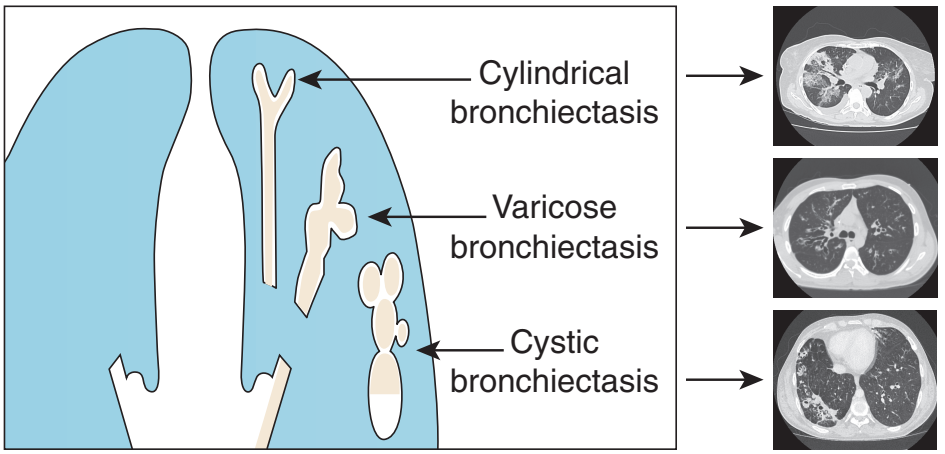


Figure 9-12. Radiology of Bronchiectasis

Treatment is conservative at first, treating the underlying cause and giving antibiotics when sputum production increases or symptoms are mild. Chest physiotherapy and postural drainage can control/improve drainage of bronchial secretions.

- Antibiotics to cover gram-negative bacteria if significant symptoms or pneumonia
- Hemoptysis: CT chest and bronchoscopy may help localize the site of bleeding; for brisk hemoptysis, bronchial artery embolization or resection surgery may be required
- Prevention with annual vaccination for influenza; pneumococcal vaccine (Prevnar 13 and/or Pneumovax 23; long-term, low-dose macrolide for patients who have >2 bronchiectasis exacerbations/year to prevent bacterial infection

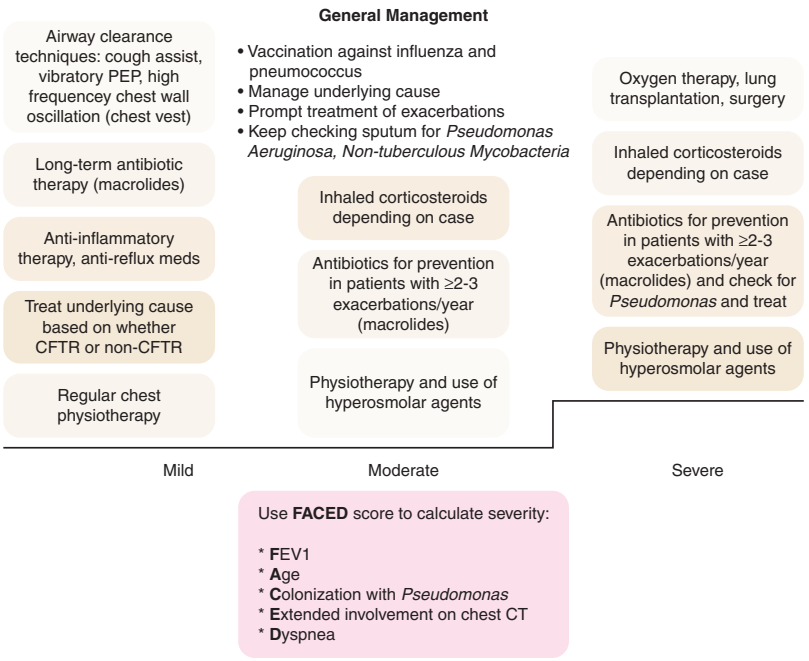


Figure 9-13. Treatment of Bronchiectasis

Going back to our earlier patient, treatment would include antipseudomonal antibiotics (ciprofloxacin, ceftazidime). Based on her history, consider a chloride test to diagnose CF.

Clinical Recall

A 17-year-old boy presents with an acute asthma attack. Which of the following patterns will be seen on an arterial blood gas?

A. $PaCO_2$ decreased, pH increased, PaO_2 normal

B. $PaCO_2$ decreased, pH decreased, PaO_2 increased

C. $PaCO_2$ increased, pH decreased, PaO_2 decreased

D. $PaCO_2$ increased, pH increased, PaO_2 increased

Answer: A

RESTRICTIVE LUNG DISEASE

Restrictive lung disease is caused by restriction of lung expansion due to extrinsic (extra-pulmonary) and intrinsic (parenchymal) pulmonary disease. On PFTs, restrictive lung disease is defined as a reduced TLC, a decrease in the forced vital capacity and FEV1 with a normal FEV1/FVC ratio.

A **normal DL_{CO}** implies **extrinsic** restrictive lung disease, while a **decreased DL_{CO}** implies **intrinsic** restrictive lung disease.

- **Extrinsic** restriction
  - Anatomical diseases: pectus carinatum, pectus excavatum
  - Musculoskeletal diseases: ankylosing spondylitis, kyphosis, scoliosis
  - Neuromuscular diseases: myasthenia gravis, Lambert-Eaton syndrome, ALS
  - Diseases restricting volume: obesity, pneumothorax, pleural effusion
- **Intrinsic** restriction (caused by interstitial lung disease)

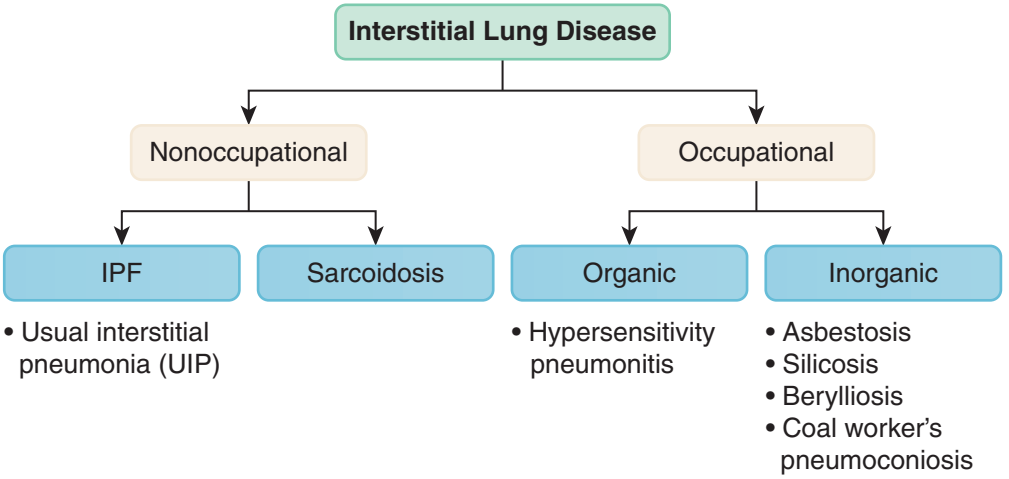


Figure 9-14. Interstitial Lung Disease

Interstitial Lung Disease

Interstitial lung disease (ILD) (or diffuse parenchymal lung disease) inflames or scars the lungs. The scarring can lead to stiffness, which in turn can make it difficult to breathe. The interstitium (supporting structure) of the lung is the tissue around the small blood vessels and alveoli.

The various interstitial lung conditions are characterized by chronic inflammation and fibrosis of the interstitium that eventually extends into the alveoli and disrupts normal gas exchange.

Symptoms include exertional dyspnea (**most common**), nonproductive cough, coarse crackles, evidence of pulmonary hypertension (increased pulmonic sound, right heart failure), and possible clubbing.

Diagnosis.

- Chest x-ray will show reticular, nodular, or reticulonodular pattern
- High resolution CT will show "ground glass" pattern and honeycombing in cases of UIP/IPF and chronic HP
- PFTs will show intrinsic restrictive pattern
- Lung biopsy if needed: bronchoscopy or open lung

Occupational interstitial disease

History is of primary importance in assessing occupational lung disease. Causes include inhalation of dust/fibers (which initiates an inflammatory process that leads to fibrosis of the lung and eventual respiratory insufficiency); organic etiologies; and inorganic etiologies.

Organic etiologies include **hypersensitivity pneumonitis (HP)** (or extrinsic allergic alveolitis), a complex syndrome of varying intensity, clinical presentation, and natural history.

- Symptoms include:
  - **Acute** HP: abrupt onset (hours following exposure) of fever, chills, malaise, nausea, cough, chest tightness, and dyspnea; first step is to remove exposure to the inciting antigen
  - **Subacute** HP: develops gradually with a productive cough, dyspnea, fatigue, anorexia, and weight loss; respiratory impairment more pronounced than with acute HP
  - **Chronic** HP: insidious onset of cough, dyspnea, fatigue, and weight loss; possible irreversible respiratory findings due to PF may be present, which is difficult to differentiate from idiopathic PF
- Pathology: poorly formed granulomas or multinucleated giant cells; chronic cellular pneumonitis with patchy lymphocytic infiltration; in chronic HP, lung pathology may resemble usual interstitial pneumonitis/IPF but with occasional granulomas or multinucleated giant cells
- **Diagnosis**: exposure history, clinical/physiologic findings, and patient's response to removal of the inciting agent; specific antibodies (precipitins) have a high false-negative rate, and positive results can be seen in exposed but asymptomatic patients; high-resolution CT shows characteristic mid-to-upper zone ground-glass or nodular opacities; BAL may confirm the diagnosis of hypersensitivity pneumonitis (a marked BAL lymphocytosis is supportive but not diagnostic)
- **Treatment**: antigen/allergen avoidance and corticosteroids (for acute); supportive care; vaccinations; pulmonary rehabilitation; long-term supplemental O_2; corticosteroids with possible steroid-sparing agents; lung transplantation evaluation (for chronic)

Inorganic etiologies include

- **Asbestosis** (pulmonary disease): parenchymal fibrosis caused by prolonged exposure >10 years to asbestos; latency period can be >30 years
  - Diagnosis: history of exposure; dyspnea on exertion (**most common complaint**); restrictive PFTs with reduced DLCO (**classic pattern**); basilar crackles with or without clubbing; radiographic lower lobe fibrosis
  - Look for ferruginous bodies (or asbestos bodies) but their presence only confirms exposure
  - Lung biopsy usually not required
  - Treatment: no effective therapy
- **Silicosis**: caused by inhalation of silica dust; seen in mining, tunneling, glass/pottery manufacturing; silica causes inflammatory reactions; symptoms are similar to asbestosis and any other pneumoconioses (except acute silicosis, caused by massive exposure, can cause lung failure in months)
  - Pathologic lesion is hyaline nodule
  - Diagnosis is made clinically; bronchoscopy with TBB and lung biopsy are confirmatory tests but are seldom done); chest x-ray will show nodules (1–10 mm) throughout the lungs but mostly in upper lobes; eggshell calcifications (rare); in progressive massive fibrosis, densities are ≥10 mm and coalesce into large masses
  - Treatment: no effective therapy; death eventually occurs because of progressive respiratory insufficiency

Note

Do not confuse **asbestosis with asbestos exposure**, which causes bilateral mid-thoracic pleural thickening/plaque/calcification formation.

In **asbestos exposure:**

- Chest x-ray will show diaphragmatic calcifications with sparing of the costophrenic angle, pleural plaques, and pleural thickening (completely benign).
- Benign asbestosis pleural effusion (BAPE) can present with a bloody effusion.
- 35% of cases have eosinophilia of pleural fluid
- Malignant mesothelioma, a tumor arising from mesothelial cells of the pleural plaques (80% of cases are associated with asbestos exposure)

- **Coal worker's pneumoconiosis (CWP)** (or black lung disease): caused by inhalation of large amounts of coal dust
  - Diagnosis: chest x-ray will show small, round densities in parenchyma, usually involving upper half of lungs; in complicated/progressive massive fibrosis, there are larger densities, from 1 cm in diameter to an entire lobe
  - When accompanied by joint inflammation and lung nodules, it is called rheumatoid pneumoconiosis or Caplan syndrome
    - Dust from the grinding of metal/rock enters the lungs, causes inflammation, and forms small lumps, leading to airway disease.
    - When someone breathes in inorganic dust, the immune system is affected and can lead to RA (where body's immune system attacks healthy body tissue by mistake).
    - When someone who already has RA is exposed to mineral dust, it can lead to rheumatoid pneumoconiosis.
  - Treatment: no effective therapy
- **Berylliosis** (or chronic beryllium disease) is a cell-mediated immune response (non-caseating granulomas of the lung) caused by exposure to even slight amounts of beryllium (high tech electronics, alloys, ceramics, pre-1950 fluorescent lights)
  - Clinically looks identical to sarcoidosis
  - Affects the upper lobes (like silicosis, TB, CWP), hilar lymphadenopathy common
  - Diagnosis: beryllium lymphocyte proliferation test (blood or BAL) (also used as surveillance tool for those who are sensitized)
  - Treatment: corticosteroids

Clinical Recall

A 65-year-old man complains of progressive difficulty breathing for 6 months. He has a 30-pack-year smoking history and is suspected of having COPD. Which of the following is the best initial management?

A. Antibiotics

B. Chest CT

C. Pulse oximetry

D. PFTs

Answer: C

Non-occupational interstitial disease

For the purposes of exam, there are 2 main types of non-occupational disease: idiopathic pulmonary fibrosis and sarcoidosis.

- **Idiopathic pulmonary fibrosis (IPF)**
  - Lungs become scarred and over time breathing becomes difficult
  - Etiology unknown
  - Main risk factors are GERD (up to 90% of patients with IPF have GERD) and chronic micro-aspiration
  - Symptoms include progressive exercise intolerance and dyspnea, coarse dry crackles ("Velcro-type rales") on auscultation, and clubbing
  - Chest x-ray will show reticular or reticulonodular disease; high-res CT will show extensive fibrosis with honeycomb pattern (referred to as a classical UIP pattern in which a biopsy is not indicated); PFTs will show restrictive intrinsic pattern; ABG will show A-a gradient widening
  - Histopathology: heterogeneous appearance with alternating areas of normal lung, interstitial inflammation, fibroblast foci, and honeycomb changes
  - **Diagnosis**: one of exclusion, after ruling out occupational exposure and drugs (bleomycin, amiodarone, methotrexate); tissue biopsy needed only for if UIP is probable or indeterminate or if non-IPF diagnosis
  - **Treatment**: supportive; consider pirfenidone (small-molecule with anti-fibrotic effects) or nintedanib (inhibitor of receptor tyrosine kinases) (equally effective; do not use both drugs together); lung transplantation (**definitive treatment**)
    - For acute IPF therapy, use a broad-spectrum antibiotic, high-dose glucocorticoid, and a cytotoxic agent (e.g., azathioprine)
    - For chronic IPF therapy, do not use glucocorticoid monotherapy or combination therapy of azathioprine, prednisone, N-acetylcysteine
- **Sarcoidosis**
  - Systemic disease characterized by the presence of non-caseating granulomas; in United States, commonly seen in African Americans and those age 20–40; etiology is unknown
    - Lung involvement (**most common**; 90% of cases)
    - Skin manifestations (common): lupus pernio, erythema nodosum, non-scarring alopecia, and papules
  - Two distinct sarcoid syndromes
    - **Lofgren syndrome** (acute): erythema nodosum, arthritis, hilar adenopathy
    - **Heerfordt-Waldenstrom syndrome** (subacute to chronic): fever, parotid enlargement, uveitis, facial palsy
  - **Diagnosis** begins with exclusion of other granulomatous diseases: hypersensitivity pneumonitis, berylliosis, infectious disease caused by mycobacteria and fungi
    - Hilar and left paratracheal adenopathy (**most common presentations, even in an asymptomatic patient**)
    - Pathology will show demonstrate noncaseating granulomas that are negative for both malignancy and infection

Note

GERD is an important risk factor for the progression of IPF. However, the classic symptoms of GERD are poor predictors of increased esophageal acid exposure seen in those with moderate/severe IPF.

- When indicated, biopsy the most accessible lesion to confirm diagnosis; since many sarcoid patients have lung involvement, this is oftentimes the initial organ to biopsy via bronchoscopy with TBB +/– EBUS
- If patient has pulmonary complaints, start with chest x-ray

– **Treatment**: glucocorticoids (mainstay of treatment for active disease)

- Three organs always treated are eyes, heart, and CNS
- The lungs, even though they are the most common organ involved in sarcoidosis, do not always have to be treated; for example, if patient is asymptomatic with mediastinal adenopathy, surveillance is sufficient
- If patient is unable to taper off steroids or worsens on steroids, use steroid-sparing agents (see Rheumatology chapter)

Sarcoidosis: Clinical Presentation

- **S**chaumann calcifications
- **A**CE levels elevated
- **R**espiratory complications/renal calculi/restrictive cardiomyopathy
- **C**alcium increase in serum and urine/CD4 helper cells (CD4/CD8 ratio >2 in early disease)
- **O**cular lesions
- **I**mmune-mediated noncaseating granulomas
- **D**iabetes insipidus/1-25 vitamin D increase
- **O**steoporosis/Osteopenia early (prednisone therapy) in some patients
- **S**kin (erythema nodosum, lupus pernio, granulomatous lesions)
- **I**nterstitial lung fibrosis
- **S**eventh cranial nerve palsy (Heerfordt-Waldenstrom syndrome)

Table 9-3. Medications Used in Sarcoidosis

Medication	Mechanism of action/Side effects
Methotrexate (MTX)	• Works by inhibiting purine synthesis by inhibiting dihydrofolate-reductase • Given orally or intramuscularly (for refractory nausea) • Always check for HBsAg and HCV antibody before initiating • Patient must take folic acid or leucovorin while on MTX
Azathioprine	• Dosing is weight-based • Toxicity is largely related to its metabolites, which are broken down by the enzyme TPMT (thiopurine-S-methyltransferase)
Leflunomide	• Works by inhibiting pyrimidine synthesis • Side effects include nausea, diarrhea, abdominal pain, hepatotoxicity
Antimalarials	• Chloroquine and hydroxychloroquine have immunomodulating properties • Mainly for cutaneous sarcoidosis; also used for hypercalcemia because it decreases 1,25 dihydroxy vitamin D • Always check G6PD level before initiating • Side effects include irreversible retinopathy and blindness (require exam at baseline and q 6–12 mos)
Mycophenolate mofetil	• Inhibitor of lymphocyte proliferation and activity • Used to treat a variety of ILDs associated with rheumatic disease • Side effects include nausea and diarrhea (may be dose limiting)
Corticotropin injection	• FDA-approved for symptomatic refractory sarcoidosis usually after prednisone and one other cytotoxic agent have failed to respond • Works on a steroid-dependent pathway and a non-steroid dependent pathway through melanocortin receptors
TNF-inhibitors	• Only infliximab and adalimumab used for sarcoidosis • Always check for latent TB, hepatitis B, and hepatitis C before initiating

OTHER PULMONARY CONDITIONS

Atelectasis

A 62-year-old man is dyspneic 24 hours after cholecystectomy. His respiratory rate is 22/min and pulse 112/min. He has a mild fever, and decreased breath sounds are noted in the left lower lobe. Complete blood count shows leukocytosis 27,000/mm^3.

Atelectasis is the collapse of lung tissue. It can be acute or chronic. It is most commonly seen in the immediate postoperative period, often secondary to poor inspiration or lack of coughing. It can also be caused by a mucous plug, tumor, or foreign body.

Symptoms in acute disease include tachycardia, dyspnea, fever, and hypoxemia. In chronic disease patients may be asymptomatic, with only x-ray abnormalities.

Diagnosis is made with chest x-ray:

- **Upper lobe** atelectasis: tracheal deviation to affected side (occurs secondary to volume loss from atelectasis)
- **Lower lobe** atelectasis: elevation of corresponding part of the diaphragm
- **Massive** atelectasis: mediastinal shift to affected side (atelectatic lobe will appear densely consolidated and smaller than normal lobe)

Treatment is deep breathing and coughing (post-operative phase), plus incentive spirometry and pulmonary hygiene for airway clearance.

For massive atelectasis that cannot be managed with minimally invasive airway clearance, do a bronchoscopy with subsequent removal of the mucous plugs.

Pleural Effusion

> A 67-year-old man presents with complaints of dyspnea and pleuritic chest pain that have worsened over the past month. He has also noticed weight loss of 20 pounds and low-grade fever during this time. On physical examination his respiratory rate is 24/min, and you find decreased air entry in the right lower lobe with dullness to percussion. Chest x-ray shows a pleural effusion involving about one-third of the lung field. A decubitus x-ray shows layering of the fluid.

Note

- On the exam, a question about pleural effusion may include buzzwords about "positive egophony," "dullness to percussion," and "decreased tactile fremitus." Do not be tempted to diagnose with those symptoms alone. Diagnostic testing is required.
- Because U/S can be easily done bedside and can guide thoracentesis and pleural tube placement, it is often the correct diagnostic test for pleural effusion.

Pleural effusion is the accumulation of fluid in the pleural cavity.

- **Transudative effusion**
  - Caused by increased hydrostatic pressure (e.g., CHF) or decreased oncotic pressure (e.g., nephrotic syndrome or cirrhosis)
  - Because conditions are **systemic**, they cause bilateral and equal effusion
  - No further evaluation needed, as it resolves with adequate treatment of primary disease
- **Exudative effusion** is caused by pneumonia, malignancy, or TB; conditions are **local**, so cause unilateral effusion; further investigation required to treat underlying disease.
  - Caused by pneumonia, malignancy, or TB
  - Because conditions are **local**, they cause unilateral effusion
  - Further evaluation needed to treat underlying disease

Symptoms of pleural effusion include SOB and pleuritic chest pain (sharp pain that worsens with breathing), secondary to the pleural effusion weighing down the diaphragm; most patients are not hypoxic despite a considerable effusion.

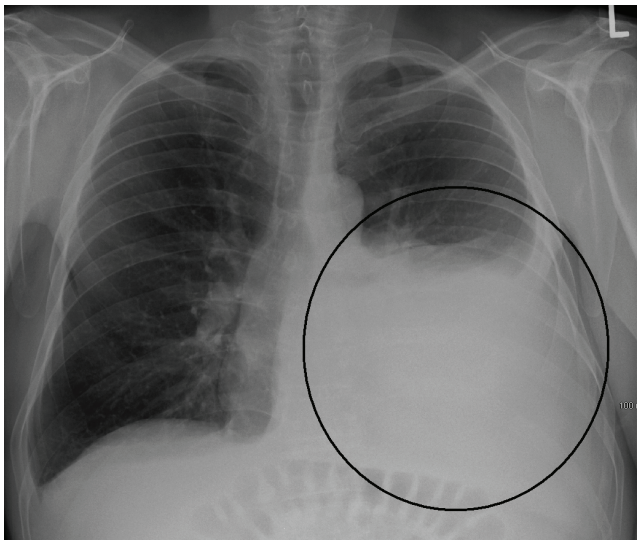
Diagnosis starts with imaging:

- PA and lateral chest x-ray (performed first)
- However, since chest x-ray cannot distinguish a density as effusion vs consolidation, consider other tests:
  - Lateral decubitus x-ray looking for free-flowing fluid which layers in the dependent pleura (however, it is possible to still have an effusion despite the lack of free-flowing pleural fluid if the effusion is loculated)
  - Chest CT (most helpful after pleural fluid is drained, to examine the lung parenchyma)
  - Ultrasound (**best test to confirm diagnosis**)
- Once the presence of fluid is confirmed, sample with thoracentesis and **classify as transudative or exudative based on Light's criteria** (biochemical analysis)
  - Get 2 tests from both the pleural fluid and the serum: lactate dehydrogenase (LDH) and protein
  - Calculate the ratios of effusion to serum to get a diagnosis
  - If even 1 criterion is positive, then it is an **exudative effusion**; all 3 criteria must be negative to be considered a **transudative effusion**

Table 9-4. Light Criteria for Exudative Pleural Effusion

	Transudative	Exudative
LDH effusion	<200 IU/mL	>200 IU/mL
LDH effusion/serum ratio	<0.6	>0.6
Protein effusion/serum ratio	<0.5	>0.5

On x-ray, pleural effusion can appear as a white area at the base of the lung.



Wikipedia, James Heilman, MD

Figure 9-15. Pleural Effusion

Clinical Correlate

When a patient has a history of CHF, do not assume that new pleural effusions are due solely to the CHF.

Treatment. Treat the underlying cause. Some common Step 2 scenarios include:

- **Parapneumonic effusion**: caused by bacterial pneumonia; a thoracentesis is required to rule out a complicated parapneumonic effusion because of the possibility of progression to an empyema (empyema requires chest-tube drainage, while an uncomplicated parapneumonic effusion will respond to antibiotics alone)
  - When a parapneumonic effusion or empyema fails to drain from a well-placed chest tube, consider possible loculations
  - Next step is to administer intrapleural tissue plasminogen activator (TPA) and deoxyribonuclease (DNase), 2×/day for 3 days; when compared with no intrapleural therapy or either agent alone, this combination therapy reduces the need for more invasive procedures
- **Malignant pleural effusion**: causes include lung/breast cancer, lymphoma; if this diagnosis is suspected, the thoracentesis fluid must be sent for cytologic examination
- **Hemorrhagic pleural effusion**: may be seen in mesothelioma, metastatic lung/breast cancer, pulmonary thromboembolism (with infarction), trauma; strongly consider a large-bore surgical tube to allow adequate drainage
- **Lymphocyte-predominant exudative pleural effusion** (**an exam favorite**): causes include malignancy and possible hypersensitivity reaction to *Mycobacterium tuberculosis* and its antigens
  - Adenosine deaminase is elevated
  - Polymerase chain reaction for tuberculous DNA is positive
  - Acid-fast stain and culture for TB are positive (<30% of cases)
  - Pleural biopsy confirms the diagnosis and is the most sensitive and specific test for pleural TB; however, this is invasive and uncomfortable

Note

PE can cause a transudative or exudative pleural effusion. If a patient has a transudative effusion with no apparent cause, consider PE.

Clinical Recall

Which of the following does not present with an exudative pleural effusion?

A. Lung cancer

B. Liver disease

C. Pancreatitis

D. Pneumonia

E. Tuberculosis

Answer: B

Acute Respiratory Distress Syndrome

A 32-year-old man is admitted to intensive care with a presumed diagnosis of gram-negative sepsis. He is placed on double gram-negative antibiotic coverage and remains stable for 24 hours. Blood cultures grow *Pseudomonas*, sensitive to both ceftazidime and ciprofloxacin, both of which have been administered to the patient. The patient seems to improve but suddenly, during day 2 of hospitalization, develops severe dyspnea. Lung examination reveals diffuse crackles; ABG shows hypoxemia and hypercarbia. Diffuse alveolar densities are seen on chest x-ray (the admission chest x-ray was unremarkable).

Acute respiratory distress syndrome (ARDS) is an acute, diffuse, inflammatory form of lung injury that has various etiologies. The classic definition of ARDS by the American-European Consensus Conference has 3 components:

- Ratio of P_aO_2/FiO_2 <200
- Acute bilateral pulmonary infiltrates
- Pulmonary capillary wedge pressure <18 mm Hg measured by Swan-Ganz catheter, or no clinical evidence of left-heart failure

The causes of ARDS include:

- **Direct causes**: aspiration (**most common**), pneumonia, inhalation injury (toxins), drug overdose, and drowning
- **Indirect causes**: sepsis (**most common**), pancreatitis, transfusion-related acute lung injury, trauma, DIC, Goodpasture syndrome (or any cause of diffuse alveolar hemorrhage), SLE, and most rheumatologic diseases

Direct and indirect ARDS are grouped together due to similarities in clinical presentation, physiology, pathology, and management.

ARDS is characterized by increased permeability of the alveolar-capillary membrane:

- Causes pulmonary edema (non-cardiogenic)
- Leads to severe hypoxemia
- Decreases pulmonary compliance
- Demonstrates accumulation of inflammatory cells and their mediators, leading to diffuse alveolar damage.

Clinical Presentation. There is a 24–72-hour lag time between injury and the development of ARDS. Symptoms include dyspnea, tachypnea, diffuse rales and rhonchi on auscultation, and severe hypoxemia. Other findings include decreased PaO_2 and normal/increased $PaCO_2$ (measured by ABG).

Clinical stages include exudative, then proliferative, then fibrotic.

Clinical Correlate

Healthy lungs regulate the movement of fluid to maintain a small amount of interstitial fluid and dry alveoli. Lung injury interrupts this balance, causing excess fluid in both the interstitium and in alveoli. Consequences include impaired gas exchange, decreased compliance, and increased pulmonary arterial pressure.

Diagnosis. The latest Berlin Definition of ARDS (2012) requires that all of the following criteria be present to diagnose ARDS. **Swan-Ganz catheter is no longer needed**.

- Symptoms must have begun within 1 week of a known clinical insult
- Bilateral opacities consistent with pulmonary edema must be present on chest x-ray or CT
- Respiratory failure must not be explained by cardiac failure or fluid overload

The severity of ARDS is defined by the severity of the hypoxemia.

- **Mild** ARDS
  - PaO_2/FiO_2 >200 mm Hg but ≤300 mm Hg
  - On ventilator settings that include PEEP or CPAP ≥5 cm H_2O
- **Moderate** ARDS
  - PaO_2/FiO_2 >100 mm Hg but ≤200 mm Hg
  - On ventilator settings that include PEEP ≥5 cm H_2O
- **Severe** ARDS
  - PaO_2/FiO_2 ≤100 mm Hg
  - On ventilator settings that include PEEP ≥5 cm H_2O

Treatment. Treat the underlying disorder, e.g., antibiotics for sepsis. Optimize cardiopulmonary support and maintain adequate cardiac output.

- Enteteral nutrition (via intestines), not parenteral
- Glucocorticoids for early ARDS (reduces duration of mechanical ventilation and length of ICU stay, but weigh risks/benefits of steroids, especially in septic patient)
- Ventilator management (no ventilator mode has proven better than any other)
  - Low tidal volumes: 6–8 mL/k ideal body weight to prevent barotrauma to lungs; caution that low tidal volumes may lead to elevated $PaCO_2$ ("permissive hypercapnia")
  - PEEP: best way to improve oxygenation is to recruit some of the fluid-filled collapsed alveoli
- Positioning: lateral decubitus, with the better functioning lung dependent to maximze profusion and improve V/Q matching

Pulmonary Nodule

A 26-year-old man is found to have a 2.5-cm calcified nodule in the right middle lung on a routine chest x-ray before starting his residency. He has never smoked and otherwise feels well. The physical examination is unremarkable. What will you recommend for this patient?

The solitary pulmonary nodule that is found incidentally on an x-ray poses a specific problem for the clinician. Around 35% of all solitary nodules are malignant.

Calcification of the nodule points toward a benign diagnosis, e.g., popcorn calcifications usually are caused by hamartomas, whereas bull's-eye calcifications are caused by granulomas.

The **first step** is to look for a **prior x-ray**. Finding the same pulmonary nodule on an x-ray done years ago may save you from doing any further workup. If no prior x-ray is available, then consider whether this patient is high or low risk for lung cancer.

- In **low-risk patients**, age <35, nonsmoker with calcified nodules but no previous history of malignancy; follow with chest x-ray/CT every 3 months for 2 years: stop testing if there is no growth after that time (based on Fleischner Society Radiology guidelines)
- **High-risk patients** age >50, smoking history, previous history of malignancy with a nodule: likely to have bronchogenic cancer

Diagnosis is based upon a multidisciplinary approach.

- Bronchoscopy (traditionally used for central lesions but more recently can reach lesions that are more peripheral)
- CT-guided biopsy or resection of a nodule intra-operatively with a frozen section (for most peripheral lesions)
- PET-CT scan (to evaluate malignancy), especially in those at moderate risk for malignancy and with a pulmonary nodule >0.8 cm
- Possible lobectomy/pneumectomy, based on pathology

Treatment. New Fleischner Society guidelines from 2017 advise a less intensive approach than before for most small pulmonary nodules discovered incidentally on CT scan.

- No follow-up for solitary nodules ≤6 mm in low-risk patients age >35 (even if multiple nodules are present)
- Surveillance up to 5 years for (slow-growing) ground-glass nodules (not solid) >6 mm with low risk for malignancy

PET scan is not recommended because these nodules are slow-growing and thus not very metabolically active.

Clinical Pearl

In all patients with a pulmonary nodule, first try to obtain an old chest x-ray.

Pulmonary Embolism and DVT

A 32-year-old woman is brought to the ED with an acute onset of shortness of breath and pleuritic chest pain that occurred while she was shopping. She has never been sick and takes no medications other than oral contraceptives. Her respiratory rate is 26/min and pulse 107/min. Auscultation is clear, and the rest of the examination is normal. ABG shows evidence of mild hypoxemia (7.52/70/25/93%). Chest x-ray is normal.

Pulmonary embolism (PE) and deep vein thrombosis (DVT)—considered one disease—are defined as an obstruction of a pulmonary artery by a particle (usually a blood clot) that has dislodged or moved from another part of the body through the bloodstream.

- **PE** occurs when a clot breaks loose and travels through the bloodstream to the lungs. The clot can block a blood vessel in the lungs, causing damage and interfering with oxygenation. Types (examples) of emboli include:
  - Fat (petechial rash post-long bone fracture)
  - Air (caisson disease [decompression sickness] seen in ascending ocean divers)
  - Thrombus (in pulmonary thromboembolism or stroke)
  - Bacterial (infective endocarditis causing septic emboli)
  - Amniotic fluid (with DIC post-delivery)
  - Tumor
- **DVT** (most common cause of PE) occurs when a blood clot forms in a deep vein of the leg (often after sitting for long periods, since lack of movement slows down blood flow). From the leg, the clot can break off and travel through the bloodstream to another area of the body.

After a proximal DVT dislodges, it travels through the vena cava and into the right side of the heart. As it goes into the pulmonary circulation, obstructing parts of the pulmonary artery, it often breaks into multiple thrombi. The result is increased alveolar dead space, vascular constriction, and increased resistance to pulmonary blood flow.

- When ~50% of the lung vasculature is involved, significant pulmonary hypertension may occur. This is followed by an increase in right ventricular workload and may lead to right-sided heart failure.
- When a PE causes hemodynamic compromise (low systolic BP), this is referred to as a **massive PE**.

Symptoms include the following:

- Sudden onset of dyspnea (shortness of breath) and tachypnea
- Thigh or calf swelling, with or without dyspnea
- Pleuritic chest pain
- Hemoptysis (only with infarction, which is rare because of the dual circulation [bronchial and pulmonary] that supports lung parenchyma)
- Tachycardia and increased pulmonic sound (P2)

Note

PE is the third most common cardiovascular cause of death in the United States, and the incidence has not declined in recent years. This may be related to inadequate DVT prophylaxis in hospitalized patients.

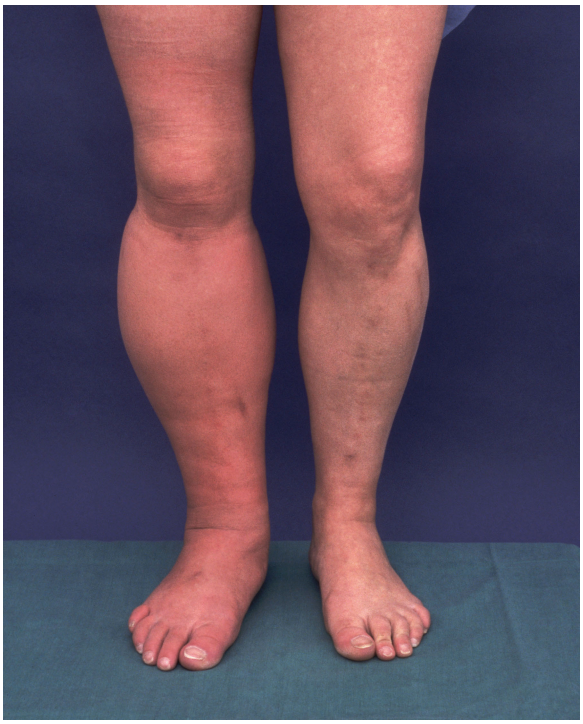
Note

Newer research shows that upper extremity DVT is a more frequent cause of PE than previously thought, especially in those with an IV catheter in internal jugular and subclavian veins.

Clinical Correlate

The circulatory system is made up of the heart, arteries, capillaries, and veins.

- The body pumps blood from the heart into the arteries, where it then flows into capillaries.
- Blood returns back to the heart through the veins. As it does this, the blood flow slows down.
- Slowed blood flow has the potential to cause clot formation; blood clotting is a normal process to prevent bleeding.



Biomedical Communications 2007—Custom Medical Stock Photo

Figure 9-16. Unilateral Right Leg Swelling Due to DVT

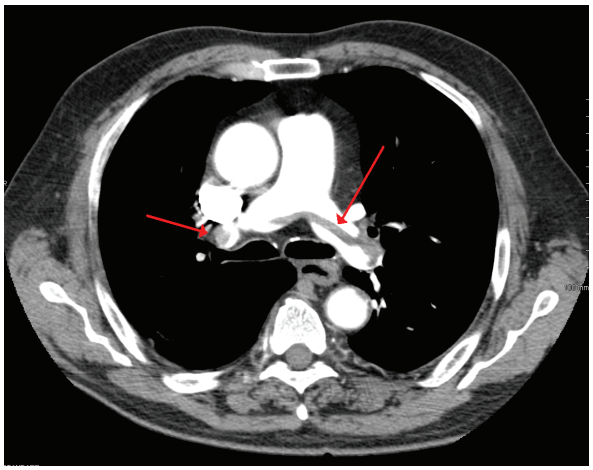
Diagnosis.

- **DVT**
  - Serum D-dimer (only if pretest probability of DVT is low; a normal D-dimer safely excludes DVT); note that it is nonspecific in chronically ill and hospitalized patients
  - Compression ultrasonography of lower extremity (**procedure of choice for the exam**)
  - Venography (invasive and not practical)
- **PE**
  - Chest CT scan with IV contrast (**plus clinical suspicion is best combination to diagnose**)
  - Other work-ups include:
    - **ABG** will show hypoxia, widened A-a gradient, and respiratory alkalosis secondary to the tachypnea from the pain (plus discomfort of a PE)
    - **Chest x-ray** (**done first**) to help rule out other causes in the differential; most often it is normal but some classic findings include "Hampton's hump" (pleural-based, wedge-shaped defect from infarction just above the diaphragm), "Westermark's sign" (lack of vascular markings in area downstream of the embolus), and "Fleischner lines" (atelectasis, pleural effusions)
    - **ECG usually done for anyone with chest pain**: right-axis deviation S1, Q3, T3 (deep S in lead I, Q wave in lead III, inverted T wave in lead III); sinus tachycardia (**most common**)

- **V/Q lung scan** (only if PE is suspected but patient cannot receive contrast): tagged albumin is injected into pulmonary circulation and then patient inhales a tagged gas that is distributed into the airways; results are not positive or negative but rather normal, low probability, moderate probability, or high probability; results must be combined with history, physical exam, pre-test probability, and other clinical information such as D-dimer and U/S results for DVT
- **Venous studies**: PE and DVT are 2 manifestations of the same disease process; once a DVT is diagnosed, assume that a PE has been diagnosed as well, because management will not change in the **acute** setting; U/S of the lower extremities is commonly ordered when tests such as CT pulmonary angiogram cannot be done in acute setting. A negative lower extremity U/S does not rule out a PE.
- **Serum D-dimer** (only for those with low pre-test probability of a PE; has a very high negative predictive value): **fibrin degradation product** (small protein fragment) present in the blood after a blood clot is degraded by fibrinolysis (main enzyme is plasmin); predicts recurrent disease after stopping anticoagulant therapy for unprovoked VTE
- **CT pulmonary angiogram** (**non-invasive "gold standard" in evaluation**), now often used in place of V/Q scan; requires contrast (renal failure is probably a contraindication in the setting of a suspected PE)
- **Echocardiogram** to determine right ventricular strain and evaluate other etiologies for symptoms; not indicated for diagnosis of PE
- **Pulmonary angiogram** (not commonly ordered in the acute setting due to the specificity and sensitivity of CT angiography for PE); invasive

Hypercoagulable workup is indicated if thrombosis is in an unusual site, is recurrent, is seen age <40, or patient has a family history. Perform 2 wks after anticoagulation has been discontinued.

- If patient clots at the hepatic or portal vein (unusual sites), evaluate for JAK2 mutations and paroxysmal nocturnal hemoglobinuria by checking CD 55 and CD 59 markers.
- If patient has thrombosis and develops warfarin-induced skin necrosis, evaluate for protein C deficiency.
- Any arterial thrombosis is unusual; one main thing to evaluate for is antiphospholipid syndrome.



Wikipedia, James Heilman, MD

Figure 9-17. Pulmonary Embolism CT

Treatment. Treatment is dictated by whether the cause is **provoked (reversible)** or **unprovoked (nonreversible)**. This is determined clinically by evaluating the patient's risk factors, which include:

- Pregnancy (increased risk for thromboembolism continues until 2 months post-delivery)
- Smoking
- Oral contraceptives (risk increases even more if patient currently smokes)
- Paroxysmal nocturnal hemoglobinuria
- Perioperative status (knee replacement surgery carries a 70% risk for DVT)
- Prolonged immobility (perioperative, extended travel)
- DM
- Age >60
- Obesity
- Nephrotic syndrome (loss of proteins C and S; antithrombin III in the urine)
- Occult cancer
- Coagulation factor abnormality ("hypercoagulable workup")
  - Factor V Leiden mutation (**most common**) (protein C resistance, not deficiency)
  - Protein C deficiency
  - Protein S deficiency
  - Antithrombin III deficiency
  - Elevated homocysteine
  - Antiphospholipid antibodies: lupus anticoagulant, anticardiolipin; β_2-microglobulin

Clinical Correlate

In patients with patent foramen ovale, venous thromboembolism may result in embolization involving the systemic circulation. This frequently presents as CVA.

Clinical Correlate

- Consider PE if the patient has dyspnea and normal chest x-ray.
- Consider PE if the patient has a transudative effusion with no apparent cause. PE can cause a transudative or an exudative pleural effusion.

To determine the pretest probability of a PE, use the Wells' criteria, which have been validated in both inpatient and emergency settings. Do these after the chest x-ray is complete. Start heparin in patients at high risk while completing the diagnostic evaluation. Exclude PE with normal CT plus D-dimer or Doppler U/S.

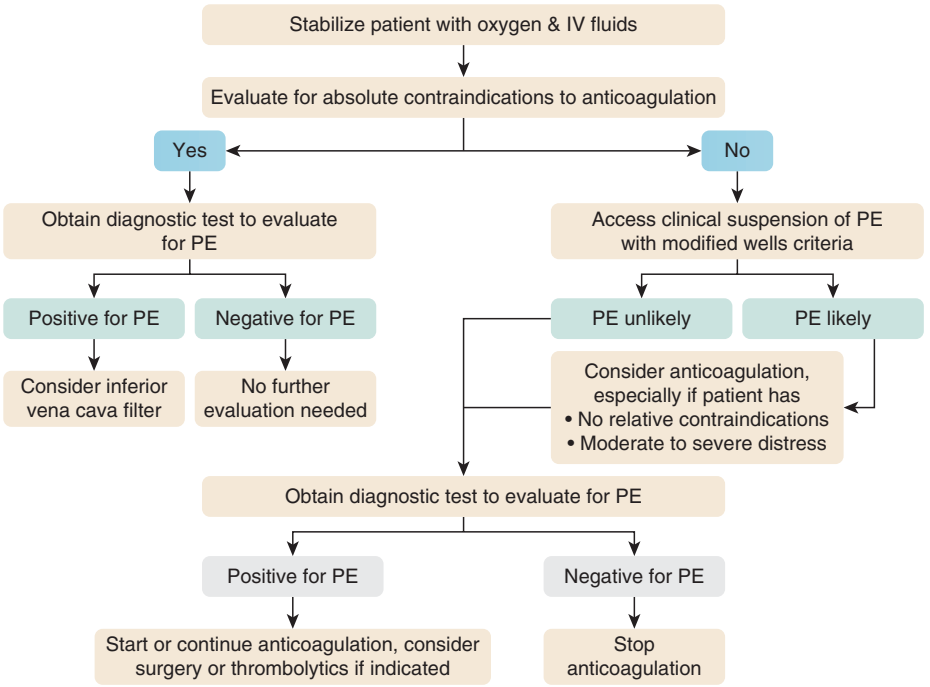


Figure 9-18. Triage Management of PE

Note

For each patient, weigh the risk of morbidity and mortality without anticoagulation against the risk of bleeding with anticoagulation.

Treatment is anticoagulation. VTE encompasses DVT and PE. The risk of recurrent thrombosis and embolization is highest in the first few days and weeks following diagnosis; therefore, initial anticoagulation on days 0–10 is critical to prevent recurrence and VTE-related death.

- Indications include patients with U/S-proven proximal DVT (popliteal, femoral, or iliac vein), most cases of symptomatic distal DVT (below the knee), and PE
- Initial anticoagulation: unfractionated heparin, low-molecular-weight heparin (high success rate), fondaparinux, or oral factor 10a inhibitors
  - Traditional treatment
    - Unfractionated heparin or low-molecular-weight heparin (you can see "HIT" with both) and monitor platelets
    - Warfarin (begin on day 1 and overlap with heparin for 5 days to maintain INR = 2–3); for warfarin-induced skin necrosis (factor 7 has shortest half-life), initiate treatment with heparin (UFH/LMWH)
  - New oral anticoagulants (direct oral anticoagulants [DOACs])
    - Factor Xa inhibitors (e.g., apixaban, rivaroxaban): often used for initial therapy because no "bridge" with heparin is required, as in the case of dabigatran
    - Direct thrombin inhibitors (e.g., dabigatran)
    - IVC filter: if anticoagulation contraindicated, if there is recurrence despite adequate anticoagulation, or if bleeding requires discontinuation of anticoagulation

- For massive PE (hemodynamic instability in the setting of a PE/DVT and persistent hypotension/severe hypoxemia despite maximum oxygen therapy)
  - Systemic thrombolytic therapy (e.g., tPA)
  - Mechanical thrombectomy if contraindications to systemic thrombolytics: catheter-directed via interventional radiology or surgical (invasive and associated with high mortality)

Bleeding Risk of DOACs vs. Heparin/Coumadin

- DOACs have lower risk of intracranial hemorrhage than warfarin
- DOACs have higher risk of GI bleed than warfarin (except apixaban, which has same risk as warfarin)
- Dabigatran has highest risk of GI bleed

Tools such as the **HAS-BLED** score can facilitate estimating the risk of bleeding in anticoagulated patients (note that no tool has been validated in anticoagulation for VTE). Prophylaxis must be weighed against bleeding risk. For the exam you will **not have to calculate the score**.

- **H**ypertension
- **A**bnormal liver/renal function
- **S**troke
- **B**leeding
- **L**abile INRs
- **E**lderly age >65
- **D**rugs or alcohol

Score >3 indicates the need for regular follow-up, but it is not an indication for termination of anticoagulation. Consider alternatives if available, e.g., IVC filter.

Clinical Recall

A 36-year-old woman presents to the ED with a sudden onset of difficulty breathing. She has a significant smoking history and is suspected of having a pulmonary embolism. Which of the following is the gold standard test?

A. ABG

B. Chest x-ray

C. D Dimer

D. Pulmonary angiogram

E. PFTs

Answer: D

Clinical Pearl

Chronic elevation of serum bicarbonate may be seen in patients with sleep apnea. This is a response to respiratory acidosis.

Note

Apnea means > 90% decrease in airflow for ≥10 seconds. **Hypopnea** is >30% decrease in airflow for ≥10 seconds with an associated decrease in oxygen saturation or an arousal.

Sleep-Disordered Breathing

Sleep-disordered breathing often includes "apnea," a pause in breathing that lasts at least 10 seconds.

Sleep apnea

- **Obstructive** sleep apnea (OSA) (**common**) is caused by an upper airway obstruction secondary to the patient's anatomy. Patients are usually obese, but that is not a necessary clinical feature. Treatment begins with lifestyle modification such as weight loss and exercise, but CPAP is the gold standard. When noninvasive measures are not effective, surgical procedures are considered.
- **Central** sleep apnea (<5%) is caused by inadequate ventilatory drive. Treatment is focused on addressing the underlying causes, which can include heart failure and medications such as opioids.

Diagnosis is done with polysomnography, at a sleep clinic or at home. Airflow is monitored, effort belts are evaluated, etc. The frequency of apnea/hypopnea determines severity of disease (adult criteria):

- **Normal** <5/hr
- **Mild** 5–15/hr
- **Moderate** 15–30/hr
- **Severe** >30/hr

Obesity hypoventilation syndrome

Previously known as Pickwickian syndrome, obesity hypoventilation syndrome is a breathing disorder affecting people suffering from obesity (BMI >30) with hypercapnia ($PaCO_2$ high, paO_2 low) even while awake.

Patients may have this condition independent of OSA. Having both conditions portends a worse prognosis.

Treatment is lifestyle modification, weight loss (consider bariatric surgery evaluation), and BiPAP (essential to treat the hypercapnia which cannot be accomplished with CPAP).

LUNG CANCER

A 65-year-old man is seen in the ED with headache and blurry vision for several days. On examination neck vein distension and darker skin color over the face and neck are noted. The patient seems confused. Chest x-ray reveals a right upper lobe lung mass. Blood tests indicate significant hypercalcemia.

Lung cancer (or bronchogenic carcinoma) is the **most common cause of death among all cancers in both males and females**, surpassing breast cancer in females and prostate cancer in males. The overall 5-year survival rate is <10%.

For the sake of staging, treatment, and prognosis, lung cancers are categorized into 2 categories: **small-cell lung carcinoma** (SCLC) and **non-small-cell lung carcinoma** (NSCLC).

- **SCLC**: faster growing than NSCLC but more responsive to chemotherapy
- **NSCLC (far more common)**
  - **Adenocarcinoma** (a very common lung cancer in the United States for both men and women)
  - **Adenocarcinoma in situ** (formerly known as bronchoaveolar carcinoma), seen primarily in non-smokers; does not have to be a solid nodule or mass
  - **Squamous cell carcinoma** (SCC), 25% of all lung cancers
  - **Large cell carcinoma**

Risk factors for any lung cancer include:

- Smoking (**most common**) and exposure to second-hand smoke
- Asbestos exposure (75× greater risk over those not exposed); mesothelioma (rare but aggressive) is caused by inhaled asbestos fibers
- Radon, arsenic, vinyl chloride, and air pollution exposure (all often overlooked)
- Genetic factors
- Infectious agents, like *Mycobacterium tuberculosis*

Pathology.

- **SCLC** (formerly known as oat-cell carcinoma due to its neurosecretory granules; recall it is derived embryologically from neural crest cells): usually centrally located (thus a common cause of veno-caval obstruction syndrome); rapidly growing tumor with early distant metastasis to extrathoracic sites such as liver/adrenal glands/bone; associated with Eaton-Lambert syndrome, SIADH, and other paraneoplastic syndromes
- **Adenocarcinoma**: usually peripherally located, metastasizes widely (to same sites as other bronchogenic tumors)
- **SCC**: usually centrally located; associated with cavitary lesions more than other bronchogenic tumors; often associated with hypercalcemia from secretion of a parathyroid hormone-like substance (paraneoplastic syndromes)
- **Large-cell carcinoma**: usually peripherally located; typically a diagnosis of exclusion based on pathologic biopsy lacking the features of adenocarcinoma, SCC, or small cell carcinoma

Clinical Presentation.

- Cough (**most common symptom at time of diagnosis**)
- Weight loss (common)
- Dyspnea
- Hemoptysis, chest wall pain, and repeated pneumonic processes (caused by postobstructive pneumonia)
- Hoarseness (indicates a non-resectable bronchogenic carcinoma)

Note

On the exam it is never wrong to order sputum cytology but clinically, it is low-yield in confirming a diagnosis.

Diagnosis.

- CT-guided biopsy or resection of the mass intra-operatively with a frozen section; consider lobectomy or pneumectomy based upon pathology
- Sputum cytology (minimally invasive): tumor must be invading the main airway in order to get a positive test
- Bronchoscopy with trans-bronchial biopsy and intra-bronchoscopic U/S (traditionally used for central lesions, but more recent navigational technology allows it to reach more peripheral lesions)
- If a pleural effusion is present based upon imaging, the next step is thoracentesis and cytologic evaluation of the pleural fluid; if no diagnosis is obtained, consider a biopsy of the pleura.
- Atelectasis on imaging may suggest airway obstruction; tumors in the airway are usually considered stage IV, except for a carcinoid tumor (classically in the bronchiole and usually has a good prognosis)
- Clinical staging requires extensive imaging. Earlier stages have better prognosis for cure with surgical resection, while later stages often require chemotherapy, radiation, and surgery.

Note

Of the bronchogenic tumors, SCC most often invades the bronchus and results in atelectasis.

Treatment requires a multi-discipinary approach; hopefully patient can tolerate complete surgical resection of the primary tumor, with negative ipsilateral and contralateral lymph node biopsies (only definitive cure).

- **SCLC**: chemotherapy (etoposide and platinum-based therapies are current treatments of choice)
- **NSCLC**: most common mutations include EGFR mutation; ALK translocation; BRAF gene mutation; and PD-L1
  - Adenocarcinoma: new targeted therapy for non-resectable disease has significantly changed the clinical course for patients
  - SCC: chemotherapy (prognosis is very poor)

In general, prognosis is good after surgical resection of early-stage NSCLC and poor for small-cell carcinoma.

Note

Lung cancer staging is beyond the scope of the exam.

Screening for Lung Cancer

As per USPSTF guidelines, screen annually for patients who have **both of the following criteria**. Use low-dose, non-contrast CT.

- Age 55–80 with a 30 pack-year smoking history
- Currently smokes or quit <15 years ago

No screening is needed if patient age >80; quit smoking >15 years ago; or has another medical problem that significantly limits life expectancy or the ability to undergo surgery.

The **risk of smoking on lung cancer is directly related to the number of pack-years**. Active smokers have significantly greater risk than nonsmokers.

Emergency Medicine 10

Learning Objectives

- List the steps to follow in basic life support (cardiopulmonary resuscitation)
- Interpret ECG strips to diagnose cardiac dysrhythmias and present the appropriate emergency management
- Answer questions about principles of toxicology and initial management with specific management for poisoning or overdose
- Describe direct and indirect complications and emergency management of acute/chronic alcohol use
- Describe the emergency management of head trauma, anaphylaxis, subarachnoid hemorrhage, burns, radiation injuries, drowning, and venomous bites/stings

BASIC LIFE SUPPORT (CARDIOPULMONARY RESUSCITATION)

A 54-year-old man is at the opera when he suddenly jumps up, clutches his chest, and falls into the lap of the woman sitting next to him.

Basic life support is the initial management algorithm of any patient who seems to have become unresponsive. Etiology is a cardiac, neurologic, or toxicologic event leading to markedly diminished responsiveness or loss of pulse.

Most causes of cardiac arrest are related to ventricular rhythm disturbance. The most common etiology of serious cardiac dysrhythmia is ischemia-related, particularly with coronary artery disease or another cardiac anatomic abnormality (especially cardiomyopathy).

Clinical presentation is any patient with diminished responsiveness that is usually sudden in onset.

- At first this is a clinically determined diagnosis. The initial step is to assess the patient's responsiveness, to make sure he is truly unresponsive and not just asleep. Call to or gently shake him (but be careful about shaking a patient who might have serious traumatic injury, particularly of the cervical spine).
- After determining that the patient is truly unresponsive, call for help (dial 911). Although it is natural to reach down to check a pulse, this is not the action that the USMLE or the American Heart Association wants you to build as a reflex. Without the ECG, defibrillator, and cardiac medication, there is very little a rescuer can do for a patient with a serious dysrhythmia beyond chest compressions and opening the airway.
- If a patient has a serious dysrhythmia such as asystole or ventricular fibrillation, there is virtually no survival if the heart has not been restarted within 10 minutes. Chest compressions just perfuse vital organs; they will not convert the arrhythmia back to normal sinus. AHA guidelines emphasize **high-quality CPR with uninterrupted chest compressions of adequate depth (5 cm, 2 in.) at 100/min** and **decreased intervals between stopping the chest compression and shock delivery**.
- Avoid excessive ventilation as it can be detrimental. ABC, according to new guidelines, is now **CAB** (excluding newborns). **Removing the 2 rescue breaths allows chest compressions to be delivered sooner. Earlier chest compressions and defibrillation are critical elements of CPR**.
  - Do **not** look, listen, feel for breathing.
  - Do check for pulse (for 10 seconds); if there is no pulse, start chest compressions (after calling 911).
  - Do not give rescue breaths first, as that has been shown to delay vital chest compressions and leads to an increase in mortality.
  - Do not perform jaw thrust, which just delays chest compression.
- After calling for help, position the patient on a firm, flat surface, and roll to be face up. Check for a pulse by feeling for 5–10 seconds at the carotid artery. If there is no pulse, perform chest compressions at 100/min, "push hard and push fast."
  - In **adults**, provide 30 compressions and then 2 ventilations, whether 1 or 2 rescuers is present.
  - In **children**, if 1 rescuer is present, perform 30 compressions and then 2 ventilations; if 2 rescuers are present, give 15 compressions and then 2 ventilations. Depth of chest compression is 2 inches or 5 cm.

Advanced Cardiac Life Support Algorithms

Note

The key to successful CPR is excellent chest compressions without interruption.

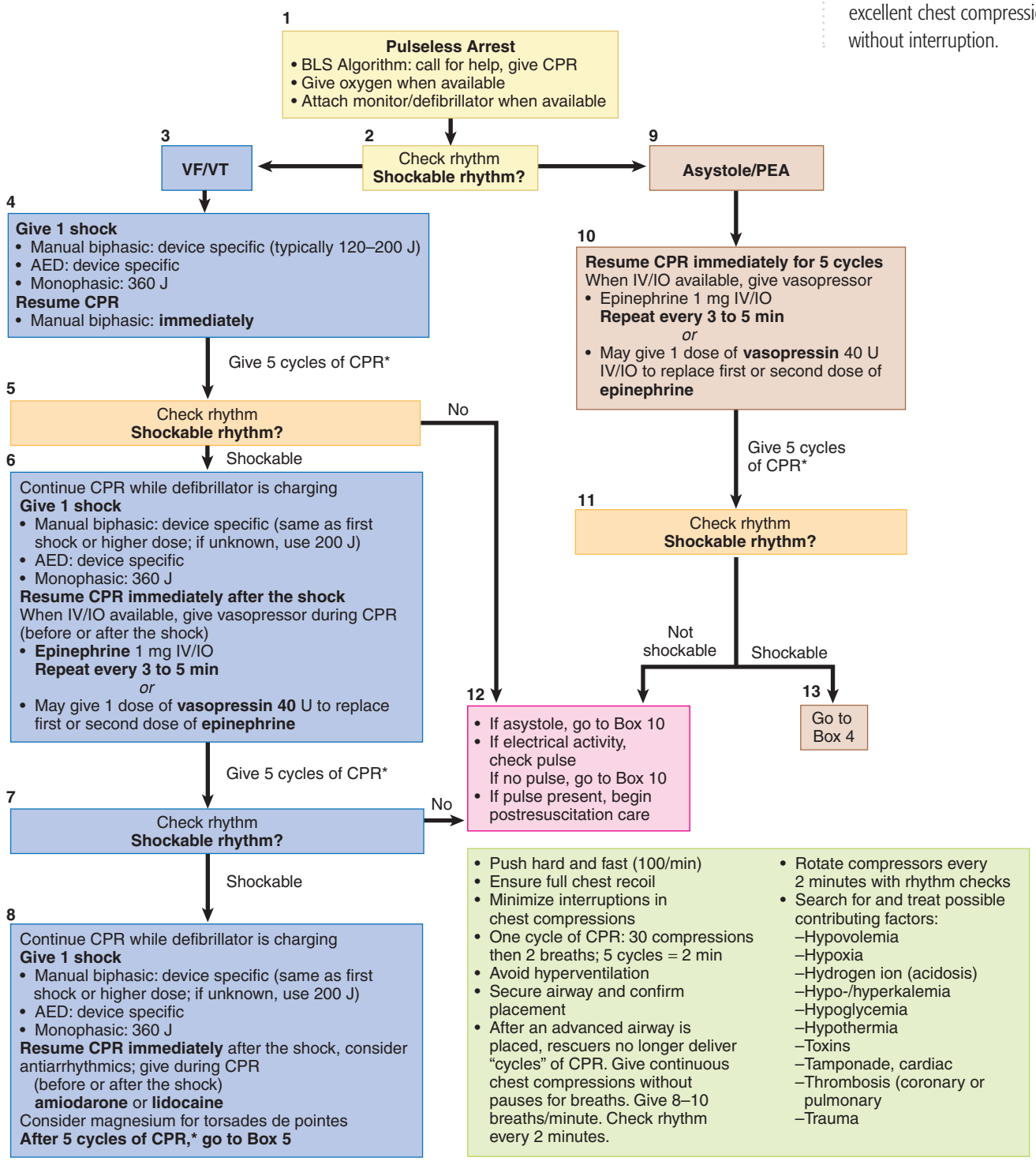


Figure 10-1. ACLS Pulseless Arrest Algorithm

CARDIAC DYSRHYTHMIAS

Asystole

A 54-year-old man is at the opera when he suddenly jumps up, clutches his chest, and falls into the lap of the woman sitting next to him. After confirming that he is unresponsive, a nearby physician performs chest compressions and ventilations. An ECG reveals no evidence of electrical activity.

Asystole is the complete absence of electrical activity in the heart. (This does not necessarily mean a completely flat line on an ECG because there may be slight variability on the rhythm strip.) Causes include:

- Ischemia and severe underlying cardiac disease (**most common causes**)
- Metabolic derangements, drug overdose, and trauma

Clinical presentation includes an unresponsive person with asystole on ECG; there is no pulse. Always confirm asystole by observing the rhythm in more than one lead on ECG.

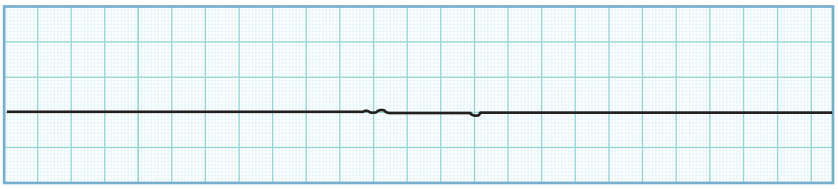


Figure 10-2. Asystole

Treatment. As you continue CPR, obtain IV access and prepare the patient for intubation.

1. Consider transcutaneous pacing only for very slow bradycardia (perform as early as possible). Pacing is not for asystole.
2. Next, administer 1 mg epinephrine via IV push every 3–5 minutes. (Atropine is no longer recommended for asystole.)
3. If asystole persists, withhold resuscitative efforts in order to evaluate the presence of atypical clinical features or cease-effort protocol.

When you see asystole on the monitor, make sure of the following:

- There are no loose or disconnected leads
- The power to ECG machine and monitor is on
- There is not a low signal gain on the monitor

Bicarbonate is useful if asystole is caused by a preexisting acidosis (except hypercarbic acidosis), tricyclic antidepressant overdose, aspirin overdose, hyperkalemia, or diabetic ketoacidosis.

Note

For asystole and other arrhythmias in this chapter, remember the "Hs and Ts":

Hypoxia

Hyper/Hypokalemia

Hypothermia

Hypoglycemia

Hypovolemia

Trauma

Toxins (including overdose)

Tamponade

Tension pneumothorax

Thrombosis (coronary and pulmonary)

Note

Atropine is no longer indicated in asystole.

Note

Transcutaneous pacemaker is not useful for asystole.

Ventricular Fibrillation

A 54-year-old man is at the opera when he suddenly jumps up, clutches his chest, and falls into the lap of the woman sitting next to him. He is not breathing. After confirming that he is unresponsive, a nearby physician performs chest compressions and ventilations. An ECG is done and reveals ventricular fibrillation. He has no spontaneous respirations.

Ventricular fibrillation is significant electrical activity on ECG with no signs of an organized pattern. The most common causes are ischemia, myocardial infarction, cardiomyopathy, and severe underlying cardiac disease. Remember the "Hs and Ts."

Presentation is a dead person with ventricular fibrillation on ECG. Diagnosis is entirely based on the ECG.

Treatment. The differences between defibrillation and cardioversion are very important.

- **Defibrillation** is a nonsynchronized delivery of shock at any phase of cardiac cycle. It is used in VF and pulseless VT. During defibrillation you depolarize all of the myocytes simultaneously, hoping that the SA node will start up normal sinus rhythm.
- **Cardioversion** is a synchronized shock with the QRS complex. When performing cardioversion, the defibrillator will not shock until the QRS complex appears. You will be able to see spikes over the QRS complexes on the monitor. If you shock on the T-wave when ventricular repolarization is taking place, you may induce VF.

Make sure that the SYN button is pushed when performing cardioversion. Use UNsynchronized shock (defibrillation) for VF or pulseless VT only.

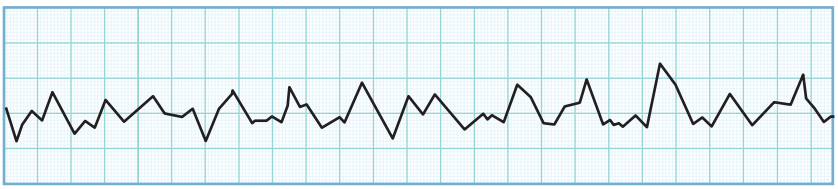


Figure 10-3. Ventricular Fibrillation

Post-Resuscitation Care. Most patients who survive resuscitation have anoxic brain injury. Therapeutic hypothermia reduces the risk of this type of severe neurologic injury. Initiate it if a patient is not following commands or showing purposeful movements. The goal of the protocol is to reach core temperature 32–34 C (90–93 F) within 6 hours and maintain for 12–24 hours. This can be done with ice packs, cooling blankets, or cold IV fluids.

Absolute contraindications for induced hypothermia are active bleeding and do-not-resuscitate order.

Note

The exact mechanism of cardiovascular collapse in an individual is often impossible to establish since patients rarely have cardiac electrical activity monitored. Research has shown that VT or VF accounts for most sudden cardiac death cases, with bradycardia or asystole accounting for the remainder.

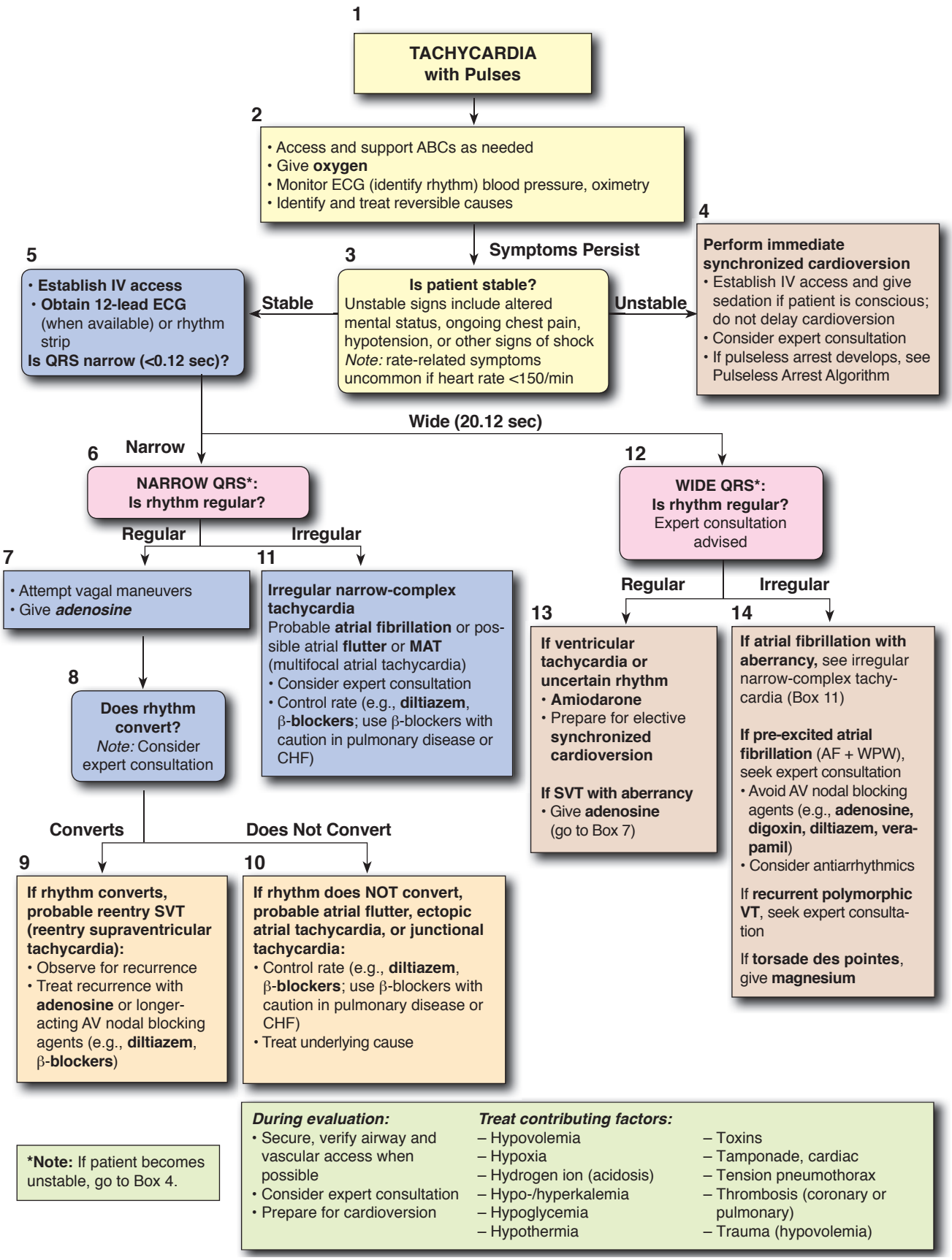


Figure 10-4. Algorithm for Tachycardia with Pulses

Ventricular Tachycardia

A 54-year-old man is at the opera when he suddenly jumps up, clutches his chest, and falls into the lap of the woman sitting next to him. He is awake but disoriented and confused, complaining of dyspnea and lightheadedness. His exam reveals jugulovenous distention and blood pressure 114/80 mm Hg. ECG shows ventricular tachycardia at rate 180 beats/min.

Ventricular tachycardia (VT) is a wide complex tachycardia with an organized, uniform pattern on the ECG. No P-waves are visible. It is most commonly caused by ischemia, myocardial infarction, and anatomic cardiac disease. Other possible etiologies include quinidine, tricyclics, phenothiazines, and long QT syndromes.

The dysrhythmia originates from an ectopic focus in the myocardium or from the AV node. When the impulse originates from around the AV node, this is from reentry. The electrical impulses must travel throughout the myocardium, from myocyte to myocyte, without the benefit of the more rapidly conducting normal pathways such as the bundle branches or His-Purkinje fibers.

The slowness of the conduction produces the slower and therefore wider complexes on ECG. The rate most often varies 160–240/min. **Torsade de pointes** is a form of VT in which the morphology varies with an undulating amplitude, making it seem that it "twists around a point." Torsade may be associated with hypomagnesemia and preceded by **long QT interval**.

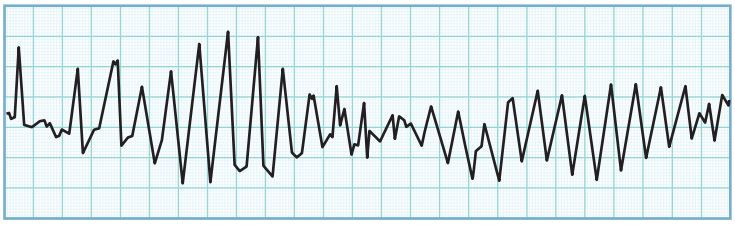


Figure 10-5. Torsade (Polymorphic VT)

Symptoms are often related to duration of the dysrhythmia. Short bursts of a few seconds may produce no symptoms at all. VT lasting >30 seconds is referred to as sustained VT. Symptoms include lightheadedness, hypotension, CHF, syncope, and death.

Diagnosis. The ECG shows the VT. For those patients presenting with syncope suspected to be of cardiac origin and in whom an arrhythmia is not visible on the initial ECG, an electrophysiologic study can be done to try to elicit the VT.

Note

Medications that prolong QT interval

- TCAs
- Antipsychotics
- Macrolides
- Methadone
- Fluoroquinolones
- Amiodarone
- Quinidine
- Class III: sotalol, ibutilide, dofetilide
- Procainamide

Causes of prolonged QT and Torsade

- Hypothyroidism
- Hypokalemia
- Hypocalcemia
- Congenital or prolonged QT syndrome

Note

Amiodarone is superior to lidocaine for VF/VT.

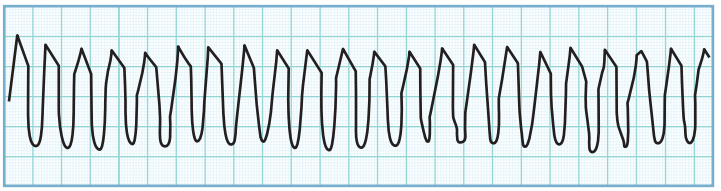


Figure 10-6. Ventricular Tachycardia (Monomorphic)

Note

If patient has sustained monomorphic VT and is hemodynamically stable after recording a 12-lead ECG, consider giving an IV anti-arrhythmic agent (amiodarone, lidocaine) and reserving electrical cardioversion for refractory patient who becomes unstable.

Treatment. For those with sustained VT and with a pulse who are hemodynamically unstable, immediate synchronized cardioversion is required. Signs of hemodynamic instability requiring cardioversion include hypotension, chest pain, altered mental status, and CHF. A lower dose of electricity, starting at 100 J, can be used at first for monomorphic VT. The cardioversion should be synchronized. Conscious patients should be sedated with midazolam, fentanyl, or morphine before cardioversion.

VT for those without a pulse should be managed in the same way as ventricular fibrillation (unsynchronized shock). Stable VT (wide, monomorphic, regular) without serious hemodynamic compromise can be treated medically with antiarrhythmics.

Magnesium may be useful in general but it is most useful for Torsade de pointes; if it fails to treat Torsade, then try isoproterenol or lidocaine. Overdrive pacing can be used if pharmacologic treatment fails. Patients undergoing cardioversion should be sedated first with medications like midazolam, fentanyl, or morphine. Long-term therapy is most effective with BBs. VT that produces sudden death or that is sustained through initial drug therapy may require the placement of an implantable cardiac defibrillator (ICD) or catheter ablation technique. All patients with ejection fraction <35% should have ICD due to increased risk of VT and VF.

Pulseless Electrical Activity

Pulseless electrical activity (PEA) is hypotension to the point of losing one's pulse; there is still some type of electrical activity on the ECG that may even be normal or a simple tachycardia. More than the other dysrhythmias, knowing the etiology PEA is the key to the therapy because the specific therapies are so divergent.

Essentially, the heart may still be beating, but there is no blood in the heart, and therefore there is no cardiac output. Causes of PEA are severe hypovolemia, cardiac tamponade, tension pneumothorax, massive pulmonary embolism, and a massive myocardial infarction. Other causes in which there may not be actual muscular contraction are hypoxia, hypothermia, potassium disorders, acidosis, and drug overdoses with tricyclics, digoxin, BBs, or CCBs.

The patient appears to be dead with no pulse. Other symptoms are based on the specific nature of what led to the PEA, such as those described. Diagnosis is made with a pulseless patient who has significantly organized, and occasionally normal, activity on ECG.

Treatment. The most important action is to maintain CPR while determining the specific origin of the PEA. General therapy includes CPR, IV access, intubation, and epinephrine. Do not shock PEA arrest. The most important therapy is repair of the cause. Bicarbonate is useful if a known acidosis has caused the arrest; it can also be used in a prolonged resuscitation if severe lactic acidosis develops and causes the refractory state of arrest.

Clinical Recall

Which of the following disorders is not an indication for cardioversion?

A. Atrial fibrillation

B. Atrial flutter

C. Electromechanical dissociation

D. Ventricular tachycardia

Answer: C

Atrial Dysrhythmias

A 24-year-old medical student is brought to the ED because of palpitations. He has been studying vigorously for the USMLE Step 2 exam and has been up for the last 24 hours. He has had 5 cups of coffee, 4 beers, 3 stimulant tablets, 2 cheeseburgers, and 1 sildenafil (Viagra). Electrocardiogram reveals an atrial dysrhythmia.

Atrial fibrillation (Afib), atrial flutter, and supraventricular tachycardia (SVT) are all characterized by an ectopic focus in the atrium or re-entry at the AV node.

- All have normal conduction in the ventricular myocardium once the impulse successfully passes the AV node and travels down the normal ventricular conduction system.
- All have a normal or narrow QRS complex and the absence of a normal P-wave.
- Afib is caused by chronic hypertension (most common), but valvular heart disease (most often mitral valve pathology), left ventricular hypertrophy, cardiomyopathy, atrial fibrosis, atrial dilation, CAD, and CHF are other causes. Another cause is toxicity causing overstimulation of the heart, i.e., hyperthyroidism, pheochromocytoma, caffeine, theophylline, alcohol, and cocaine. Drug toxicity (such as digoxin), pericarditis, pulmonary embolism, surgery, chest wall trauma, or ischemia can also cause atrial dysrhythmias.
- SVT is caused by a re-entrant mechanism around or within the AV node.

Clinical Presentation. Symptoms vary on the basis of the duration of the disorder, the ventricular rate, and the underlying health of the heart.

- With a normal heart, only 10–20% of cardiac output is directly derived from the contribution of atrial systole.
- With a dilated or postinfarction heart or with significant valvular disease, this contribution may rise to 30–40%, in which case more severe symptoms arise: from complete absence to palpitations to lightheadedness, hypotension, disorientation, CHF, and syncope.
- Rate-related symptoms are unlikely in those with heart rate <150 per minute in atrial dysrhythmia.

Note

Afib, atrial flutter, and SVT are discussed as a group because their initial management has considerable overlap.

Narrow complex tachycardia is always atrial in origin (QRS <0.12 sec). Wide complex tachycardia can be atrial or ventricular. For example, it is very difficult to distinguish Afib in the presence of LBBB and VT. The key is that in Afib with LBBB, the rate is irregular on ECG, whereas in VT it is regular. If in doubt, treat as VT.

Diagnosis. Initially, the diagnosis is based entirely on the ECG. Other patients may need a 24–72 hour Holter monitor to detect brief paroxysms of the dysrhythmia not seen on the initial brief ECG.

Note

- Narrow complex tachycardia is *always* atrial in origin (QRS <0.12).
- Wide complex tachycardia can be atrial or ventricular in origin.

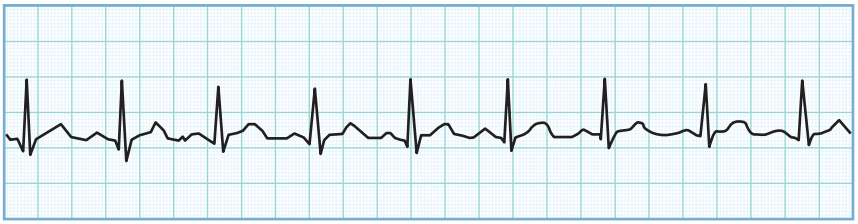


Figure 10-7. Normal Sinus Rhythm

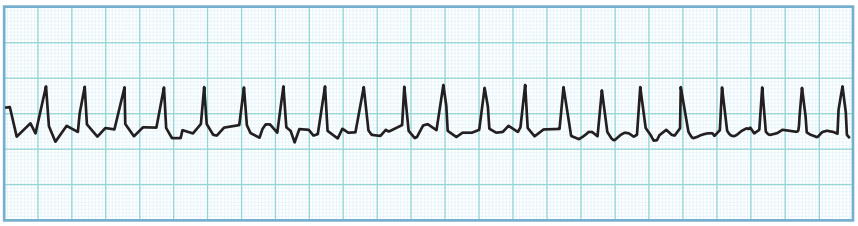


Figure 10-8. Atrial Tachycardia

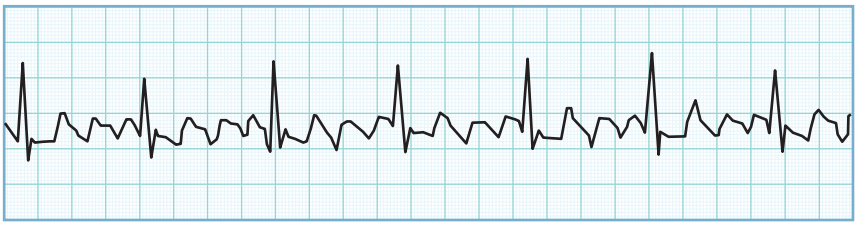


Figure 10-9. Atrial Flutter

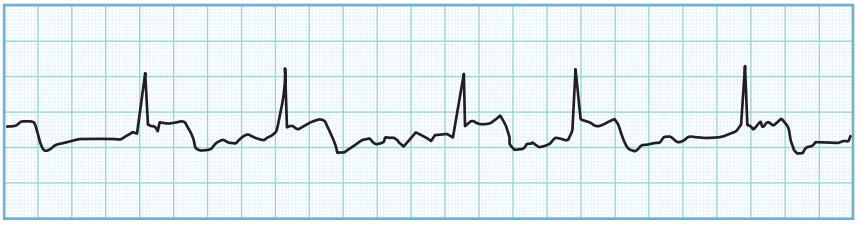


Figure 10-10. Atrial Fibrillation

Treatment. Initial therapy is based on whether there are signs/symptoms of severe hemodynamic compromise, such as hypotension, confusion, CHF, or chest pain. If there are signs, perform immediate synchronized cardioversion.

If the patient is hemodynamically stable, then the first step is to control the ventricular rate. For SVT, a vagal maneuver such as carotid sinus massage, Valsalva, or ice water immersion is most effective.

- The modified Valsalva maneuver is more effective than the standard technique: **do Valsalva followed by supine repositioning and immediate passive leg raise**.
- Do not do carotid sinus massage bilaterally.
- Do not do carotid massage on patients with carotid bruits.

If vagal maneuvers do not work, treat SVT with several rapid IV infusions of adenosine. (Do not use adenosine in patients with asthma or COPD, as it can cause bronchospasms.)

If adenosine is not effective, use a CCB (diltiazem or verapamil), BB, or digoxin to slow the heart rate.

- Try to avoid verapamil in patients with severe left ventricular dysfunction and low ejection fraction.
- Be cautious using BBs if there is a history of reactive airway disease.

After the rate has been lowered <110/min, conversion of the rhythm to normal sinus does not need to be routinely done. Chronic rate control with anticoagulation with warfarin to INR 2–3 is superior to converting the patient into sinus rhythm. Returning the patient to a normal sinus rhythm is preferable because chronic Afib can result in embolic stroke (5–7% of patients per year).

Amiodarone, ibutilide, propafenone, and dofetilide can all convert a minority of patients to sinus rhythm. (At the level of the Step 2 exam, you will not need to know much about the specific indications for each, though you will need to know that elective cardioversions should be preceded and followed by several weeks of anticoagulation with warfarin.)

Avoid adenosine in asthma and COPD, as it can cause bronchospasms.

Rate Control vs. Rhythm Control. When patients present in Afib with rapid ventricular response, hemodynamic stability must first be determined.

- If hemodynamically stable: rate-control with AV nodal blocking agents
- If unstable, do immediate synchronized cardioversion

With long-term management, rate control and anticoagulation are preferred over rhythm control. Consider **rhythm control** for the following:

- Symptomatic patients on rate control (poor exercise tolerance)
- Younger patients with normal heart structure and function
- Patients unable to be rate controlled with AV nodal blocking agents

It is very difficult to keep patients with structural heart disease in normal sinus rhythm. Several studies have shown an increase in overall mortality with rhythm control. Catheter-directed ablation of the AV node or accessory pathway may be used when pharmacological treatment fails to control rate.

Note

Palpitations and **lightheadedness** are **not signs of hemodynamic compromise**.

Note

For patients with **Afib and flutter**, give **rate control treatment plus anticoagulation** (aspirin, warfarin, etc.). When warfarin is used, optimal INR therapeutic range is 2.0–3.0.

The **rate control** goal is HR <110/min. Diltiazem, BBs, verapamil, and digoxin may help.

- Most patients require combined therapy: BBs with digoxin have been shown to be best combination.
- In patients with decompensated CHF: use digoxin first and amiodarone as second-line therapy; start BBs once patient is euvolemic on exam but use caution.

Agents for chemical cardioversion in Afib include amiodarone, dofetilide, flecainide, ibutilide, propafenone. In CHF patients, use amiodarone and dofetilide only.

Agents for maintaining sinus rhythm include flecainide, propafenone, sotalol, dronedarone, dofetilide, and amiodarone. To maintain normal sinus rhythm in CHF patients, use only amiodarone or dofetilide. In patients with coronary artery disease and normal EF, dofetilide, dronedarone, and sotalol are first line over amiodarone.

Note

CHADS2–VASc score

CHF: 1 point

HTN: 1 point

Age ≥75: 2 points
(age 65–74: 1 point)

DM: 1 point

Prior stroke/TIA: 2 points

Female sex: 1 point

Vascular disease (CAD, PAD): 1 point

The CHADS2–VASc score is used to determine if a patient with non-valvular Afib needs anticoagulation.

- **Score 0**: no treatment
- **Score 1**: aspirin or anticoagulation
- **Score ≥2**: anticoagulation

Dabigatran, rivaroxaban, and apixaban are newer agents that produce similar or lower rates of both ischemic stroke and major bleeding compared with warfarin.

- Dabigatran is an oral direct thrombin inhibitor shown to reduce the incidence of ischemic stroke compared with warfarin, with similar rates of bleeding.
- Rivaroxaban is an oral factor Xa inhibitor.
- Apixaban, another oral factor Xa inhibitor, may be used instead of warfarin for stroke prophylaxis in patients with Afib and high risk of stroke (CHADS2 score ≥2).

Note

For anticoagulation, use warfarin, dabigatran, or rivaroxaban.

Advantages of the newer agents include convenience (no requirement for routine testing of the international normalized ratio), 50% less intracranial bleed than warfarin, and less susceptibility to dietary and drug interactions. Disadvantages include lack of an antidote and the potential that new side effects may be seen over time.

For patients undergoing elective cardioversion, first determine if they have been in Afib for >48 hours. If they have, there are 2 options:

- Transesophageal echo can be done to exclude a clot; then, cardioversion (electrical or chemical). Cardioversion should be followed by 6 weeks of warfarin.
- Warfarin can be administered for 3 weeks before electrical or chemical cardioversion. Cardioversion should be followed by another 6 weeks of Coumadin.

Note

If a patient doesn't want to check INR or has difficulty staying in therapeutic range, give a newer agent.

It is very difficult to maintain patients with structural heart disease in NSR, and most convert back into Afib. Atrial flutter is managed the same way as atrial fibrillation.

Note

Patients with Afib and thyrotoxicosis always get anticoagulation until euthyroid and back in NSR.

For patients in Afib with Wolff-Parkinson-White syndrome, administration of drugs that slow AV node conduction (Ca-channel blockers, digoxin) is strongly contraindicated, as they can induce VT. Procainamide, ibutilide, flecainide, or amiodarone can be used in such cases.

If none of the medications described can successfully convert the patient to a normal sinus rhythm, then elective electrical cardioversion can be attempted. This too must be preceded and followed by several weeks of anticoagulation if the Afib has been present for >48 hours. Transesophageal echo can be done to exclude a clot and allow the cardioversion without preconversion anticoagulation. Neither medical nor electrical cardioversion can permanently maintain the majority of patients on sinus rhythm. Most convert back into atrial fibrillation.

Bradycardia

> A 48-year-old manager comes for advice about vaccinations and travel medicine before traveling overseas. He feels well and has no symptoms. He takes no medications. On examination you find blood pressure 118/76 mm Hg and pulse 40/min.

Bradycardia is a slow heart with rate <60 beats/min.

- **Sinus bradycardia** can be a normal phenomenon, particularly in trained athletes. Medications such as BBs can cause it without serious sequelae. Symptomatic sinus bradycardia from sinus node disease can be from degeneration of the node or from ischemia.
- More **serious types of bradycardia** can be from Mobitz type II second-degree heart block and third-degree (complete) heart block. These can occur secondary to ischemic damage of the AV node. Other causes are myocarditis, infiltrative disease such as amyloidosis or sarcoidosis, or neoplasms.

Clinical presentation can range from the lifelong absence of symptoms to severe symptoms of hypotension and decreased cardiac output. Diagnosis is made with ECG.

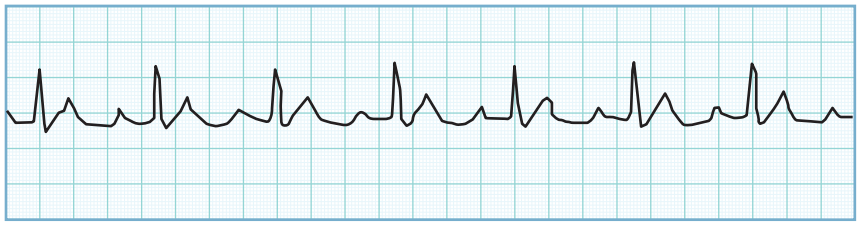


Figure 10-11. First-Degree Heart Block

Note

Mobitz type I second-degree block is characterized by **progressive** P-R lengthening, whereas **Mobitz type II** is characterized by a **constant** P-R interval.

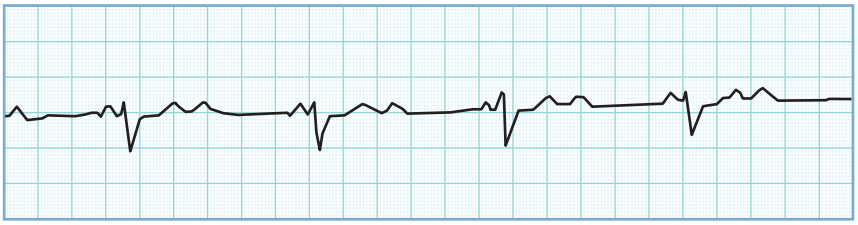


Figure 10-12. Second-Degree Heart Block

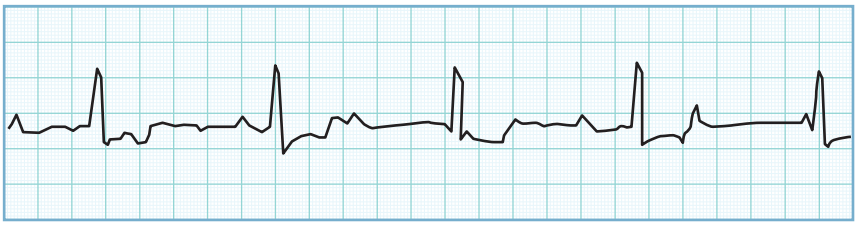


Figure 10-13. Complete Heart Block

Note

In the acute setting, transcutaneous pacing is always preferred over transvenous pacing.

Note

If the patient is on a BB, give glucagon. If the patient is on a CCB, give calcium.

Treatment. Asymptomatic sinus bradycardia, first-degree AV block, and Mobitz type I (Wenckebach) second-degree AV block often need no specific therapy. Any form of severe symptomatic bradycardia is treated initially with atropine and then a pacemaker, if there is no improvement in symptoms.

Mobitz type II second-degree block and third-degree block require the placement of a pacemaker, even in the absence of symptoms. Dopamine or epinephrine is used to improve blood pressure if there is still hypotension after the use of atropine.

For symptomatic sinus bradycardia, treatment is atropine. If atropine fails, then use transcutaneous pacing.

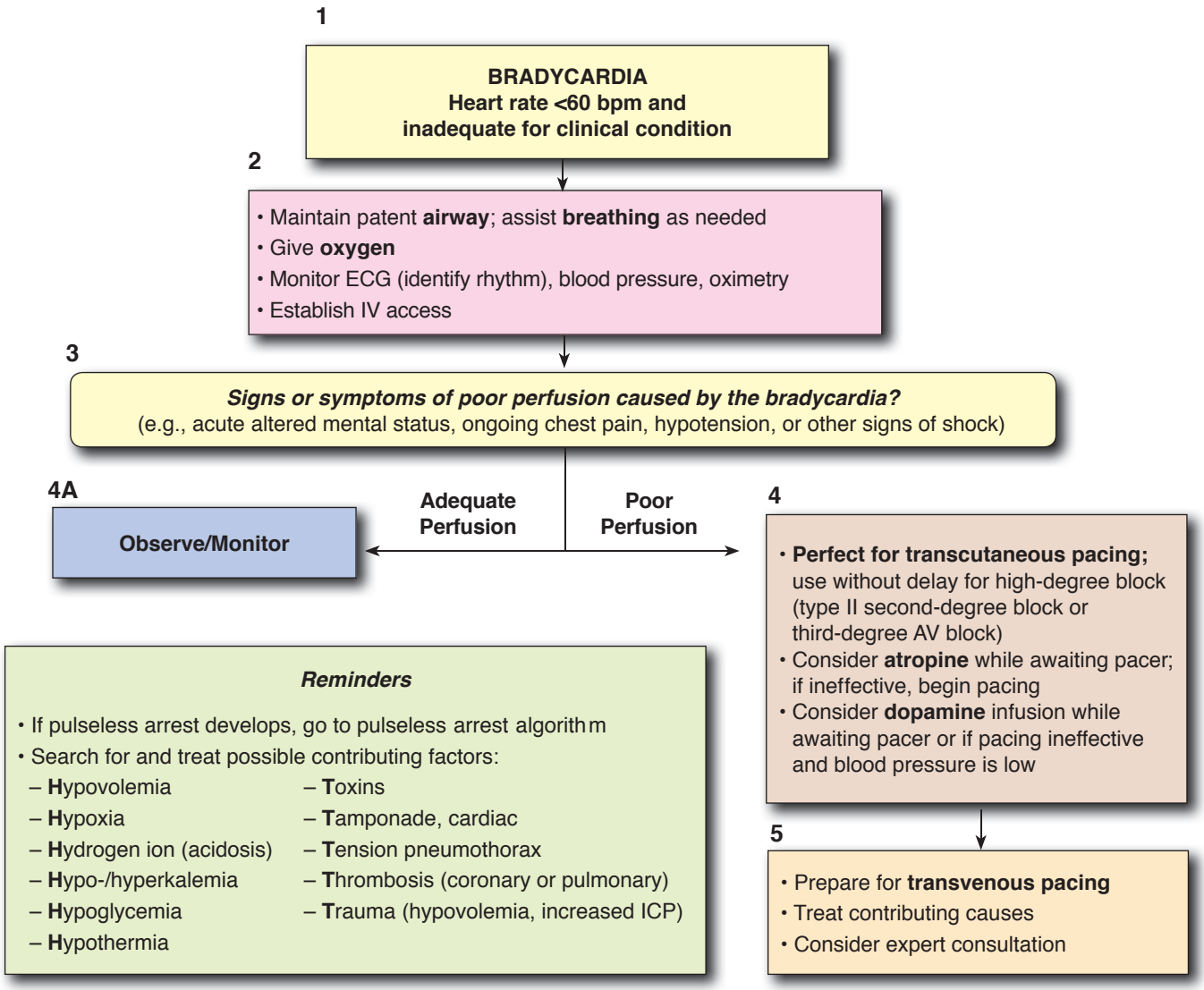


Figure 10-14. Algorithm for Bradycardia

Clinical Recall

Which of the following medications causes a prolongation of QT interval?

A. Amoxicillin

B. Erythromycin

C. Isoniazid

D. Vancomycin

Answer: B

TOXICOLOGY

A 25-year-old medical student goes home after class and finds no phone messages from his girlfriend. In a fit of despair he takes a full bottle of pills in an attempt to commit suicide. He takes the label off the bottle to prevent any attempt to reverse the poisoning through the identification of the specific agent. A few minutes later his girlfriend calls, after which time he runs to the nearest ED and states that he has changed his mind and wants to live after all. He says that he took the pills 30 minutes ago but won't tell you the specific name of what he took.

The initial evaluation of a patient who has been poisoned involves attempting to find out the nature of the toxin ingested. At the same time, history and physical examination can provide clues. In this case, the key issue is the short time between the ingestion and the arrival at the ED. The patient is awake.

Toxidromes

Note

Use caution with toxidromes, as many symptoms are common in more than one class (or can even be absent).

Toxidromes (*toxic* + *syndromes*) are groups of "common symptoms" associated with exposure to a particular class of poison. They are useful in that they help clinicians to narrow down the possible poisons involved.

Table 10-1. Common Toxidromes

Class	Physical Finding
Clonidine, barbiturates, opiates, cholinergics, pontine stroke	Miosis
Sympathomimetics, anticholinergics	Mydriasis
Anticholinergics	Dry skin
Cholinergics	Wet skin
Barbiturates, carbon monoxide poisoning	Blisters

Toxic Ingestion or Overdose

Gastric emptying is rarely, if ever, utilized. In ingestion of an unknown type, perform a urine or blood toxicology screen, but do not delay the administration of antidotes, charcoal, or gastric emptying (rarely needed).

- Activated charcoal (**mainstay of therapy**) every 2–4 hours to block further absorption of the substance and accelerate removal of toxins already absorbed by the body; charcoal is safe for all patients
- Induced vomiting with ipecac syrup, useful for ingestions in the home where the time period since ingestion is short and there are no other effective modalities available (must be done within 1–2 hours so it has no use in the hospital setting); ipecac is never recommended for children
- Lavage, i.e., gastric emptying with a large-bore (37–42 French) oropharyngeal hose (e.g., Ewald tube) only if there is altered mental status because of possible aspiration. Endotracheal intubation beforehand is typically required.
  - Lavage decreases absorption by 52% at 5 min, 26% at 30 min, and 16% at 60 min.
  - The exact indications for lavage are not clear, but the contraindications are very clear: useful only within the first hour after ingestion, and contraindicated with the ingestion of caustic substances such as acid or alkalis.
- Whole bowel irrigation, for large-volume pill ingestion where the pills can be seen on x-ray. A gastric tube is placed and high-volume (1–2 liters per hour) GoLYTELY (polyethylene glycol) is administered until the bowel movements run clear.
- Dialysis (rarely needed) only with profoundly serious symptoms such as coma, hypotension, or apnea, especially when renal/hepatic failure limits the usual means of excreting substances from the body. Hemodialysis is 20× more efficacious at removing drugs from the body than peritoneal dialysis.
- Cathartics
  - Use with charcoal administration; otherwise, they are almost never helpful.
  - On the exam, if cathartics appear as an answer choice, they are generally the wrong answer.
- Forced alkaline diuresis to eliminate salicylates and phenobarbital
  - Otherwise, simply making the patient urinate in high volumes is not helpful.
  - On the exam, forced diuresis is generally the wrong answer—except for salicylates and phenobarbital.
- Naloxone/dextrose/thiamine (**first-line** when there is altered mental status [particularly confusion] or coma)
  - Naloxone has almost no side effects and works instantly; because of its rapid response, it is both therapeutic and diagnostic.
  - Dextrose is very effective at preventing permanent brain damage from hypoglycemia.
  - It does not matter whether the dextrose or thiamine is given first.
- Benzodiazepines (**first-line for any toxin-related seizure**). If no response, use barbiturates next. Phenytoin and fosphenytoin are not indicated or even effective for this type of seizure.

Note

- Ipecac syrup is never used by physicians. It must be used within the first 2 hours of ingestion, and very few people arrive within the first hour.
- Lavage has almost no utility.

Note

Charcoal does not bind to some substances **(PHAILS)**:

Pesticides

Heavy metals

Acid/alkali/alcohol

Iron

Lithium

Solvents

Note

Substances/drugs that may require hemodialysis for removal include **(I STUMBLE)**:

Isopropanol

Salicylates

Theophylline

Uremia

Methanol

Barbiturates

Lithium

Ethylene glycol

Toxicology screen

Toxicology screen can determine the approximate amount and type of legal and/or illegal drug a person has taken. It is used to screen for drug abuse, monitor a substance abuse problem, and evaluate drug intoxication for overdose.

- The **best initial test** in toxicology screen is the urine immunoassay (qualitative test). Typically screened are alcohol, cocaine, PCP, amphetamines, and cannabinoids.
- The **confirmatory test** is gas chromatography/mass spectrometry, which provides qualitative analysis and allows identification of the specific drug or its metabolites.

Toxicology screen must be done within a certain amount of time after the drug is taken or while metabolites can still be detected in the body. Some examples of clearance time are:

Alcohol	3–10 hrs
Amphetamines	24–48 hrs
Barbiturates	up to 6 wks
Benzodiazepines	up to 6 wks with heavy use
Cocaine	2–4 days; up to 10–22 days with high level use
Codeine	1–2 days
Heroin	1–2 days
Hydromorphone	1–2 days
Methadone	2–3 days
Morphine	1–2 days
Phencyclidine (PCP)	1–8 days
Tetrahydrocannabinol (THC)	6–11 wks with heavy use

DRUG OVERDOSE

Drugs of Abuse

Opiates

Opiate toxicity is predominantly respiratory related, via depressant effects upon the respiratory centers in the brainstem. Death can occur through acute respiratory acidosis. In addition to their analgesic and euphoric effects, opiates also cause pupillary constriction, constipation, bradycardia, hypothermia, and hypotension.

Opiates can be rapidly reversed by naloxone. Since opioids decrease gastric emptying by relaxation of smooth muscle, gastric lavage may be used in cases of overdose with oral agents.

Although withdrawal of opiates is uncomfortable, it is not fatal. It is usually treated with methadone or buprenorphine.

Opiate withdrawal symptoms are the following.

- **3–4 hours**: fear, anxiety, drug craving
- **8–14 hours**: insomnia, yawning, rhinorrhea, diaphoresis, mydriasis, anxiety
- **1–3 days**: tremor, muscle spasms, vomiting, diarrhea, tachycardia, chills, piloerection

Cocaine

Cocaine blocks the reuptake of norepinephrine and other catecholamines at the synapse. This leads to a wide variety of euphoric and toxic effects. Amphetamines work in a similar way but are less likely to produce severe toxicity or death. Severe toxicity from cocaine is far more likely with smoked ("crack") or injected cocaine rather than snorted (inhaled).

Clinical Presentation. Toxic effects of cocaine are related to a very significant alpha-adrenergic stimulatory effect, resulting in the following (may lead to death):

- Very high BP
- Hemorrhagic stroke
- Subarachnoid hemorrhage
- Myocardial infarction
- Arrhythmia
- Seizures
- Metabolic acidosis, rhabdomyolysis, and hyperthermia in some cases
- Pulmonary edema (specific to smoked cocaine)

Treatment. There is no specific drug to reverse cocaine toxicity. Benzodiazepines such as diazepam are used to control acute agitation. Combined alpha/beta agents such as labetalol or alpha-blockers such as phentolamine are useful to control hypertension. Avoid pure beta-blockers because they lead to unopposed alpha stimulatory effects.

Cocaine withdrawal can cause depression as a result of the norepinephrine depletion. There is limited physiologic withdrawal from cocaine.

Benzodiazepines

Benzodiazepines (BZDs) produce somnolence, dysarthria, ataxia, and stupor. Very infrequently, they lead to death from respiratory depression; most deaths are associated with ethanol or barbiturate ingestion.

Patients receiving prolonged parenteral administration of BZDs are at risk for propylene glycol poisoning (used in parenteral formulations of diazepam and lorazepam). Rarely, this may cause hypotension, cardiac dysrhythmias, lactic acidosis, seizures, or coma.

Treatment. Good supportive care and monitoring are the foundation of treatment. As with any overdose, the first step is to stabilize the patient's airway, breathing, and circulation.

- Flumazenil is a specific antidote for BZD poisoning, although its use in acute BZD overdose is controversial.
- In long-term BZD users, flumazenil may precipitate withdrawal and seizures.
- In BZD use for a medical condition, flumazenil may exacerbate the condition.

BZD withdrawal can be similar to the symptoms of alcohol withdrawal. Although rare, deaths have been reported from severe withdrawal. The recommendation for treatment of severe forms of withdrawal is the administrations of BZDs.

Barbiturates

Barbiturates are a class of drugs with various long- and short-acting agents. Massive overdose can result in death from respiratory depression or CNS depression.

- Can cause hypothermia, loss of deep tendon reflexes, and loss of corneal reflexes
- Could result in a coma simulating brain death
- May lead to absent EEG activity
- Withdrawal may result in seizures similar to alcohol or benzodiazepine withdrawal
- Have no specific antidote, although urinary excretion of phenobarbital can be increased with the use of bicarbonate (similar to treatment for salicylate intoxication)

Hallucinogens

Hallucinogens include a variety of agents such as marijuana, LSD, mescaline, peyote, and psilocybin. Although they may cause delirium and bizarre behavior, the adverse effects are often limited to their anticholinergic effects: flushed skin, dry mouth, dilated pupils, and urinary retention.

The only hallucinogen associated with a potentially fatal outcome is the artificially created, dissociative, anesthetic phencyclidine (**PCP** or "angel dust"), which may cause seizures.

Treatment for severe hallucinogen intoxication is with benzodiazepines.

Clinical Recall

A 19-year-old man is brought to the ED in an unconscious state after consuming an unknown substance at a party. What is the next best step in management?

A. CT scan of the brain

B. Intubation

C. IV insulin

D. Naloxone/dextrose/thiamine

E. Video EEG

Answer: D

Lithium

Lithium is a commonly used medication for the treatment of bipolar disorder and acute mania. Although effective, it has a narrow therapeutic window and is associated with toxicity.

- In **acute poisoning**, patients do not have a lithium burden
  - Symptoms are primarily GI, with nausea, vomiting, cramping, and possible diarrhea
  - Progression can involve neuromuscular signs: tremulousness, dystonia, hyperreflexia, and ataxia
  - Most common electrocardiographic finding is T-wave flattening
- In **chronic poisoning**, patients have a large body burden of lithium
  - Symptoms are primarily neurologic, with mental status often altered
  - Progression can lead to coma and seizures if diagnosis is unrecognized
  - May be difficult to treat
  - Usually precipitated by introduction of new medication that may impair renal function or cause hypovolemic state

Three major drug classes have been identified as **potential precipitants of lithium toxicity**:

- Diuretics which promote renal sodium wasting
- ACE inhibitors, which reduce glomerular filtration rate (GFR) and enhance the tubular reabsorption of lithium
- NSAIDs, which reduce the GFR and interrupt renal prostaglandin synthesis

Systemic effects include renal toxicity:

- Nephrogenic DI (most severe manifestation)
- Impaired sodium and water absorption, caused by inhibition of action of antidiuretic hormone on distal renal tubule
- Renal tubular acidosis, chronic tubulointerstitial nephritis, and nephrotic syndrome

The most common endocrine disorder secondary to chronic toxicity is hypothyroidism. Lithium is taken up by thyroid cells and blocks thyroid hormone release from thyroglobulin, which inhibits adenylate cyclase and prevents TSH from activating thyroid cells via the TSH receptor. Acute exposure to lithium can cause leukocytosis, whereas chronic exposure can produce aplastic anemia.

Elevated lithium in the blood will confirm toxicity, although levels may not correlate with clinical symptoms. Serial levels may be warranted in cases of sustained-release tablets.

Treatment. Supportive therapy is the mainstay of treatment. Gastric lavage may be attempted if patient presents within 1 hour of ingestion.

- Airway protection is crucial due to emesis and risk of aspiration.
- Seizures can be controlled with BZDs, phenobarbital, or propofol.
- Fluid therapy is crucial to restore GFR, normalize urine output, and enhance lithium clearance.

Lithium is readily dialyzed because of water solubility, low volume of distribution, and lack of protein binding. Thus, hemodialysis is indicated for patients who have renal failure (and unable to eliminate lithium) and patients who cannot tolerate hydration (e.g., those with CHF, liver disease, or severe toxicity meaning neurologic symptoms >4 m/Eq/L).

Lithium is a monovalent cation that does not bind to charcoal, so activated charcoal has no role.

Salicylates (Aspirin)

> An older woman with osteoarthritis comes to the ED with dyspnea, intractable nausea, vomiting, and tinnitus. She is fully alert and able to give a good history. Her only other problem is hypertension. She is on a wide variety of medications to reduce her pain. Her husband says she was in so much pain lately that she took half a bottle of extra pills 30 minutes ago.

Salicylate intoxication results from the ingestion of a large amount of aspirin and other salicylate-containing medications, resulting in a complex, systemic toxicity.

Salicylates are complex metabolic poisons. The most common presentation is GI distress such as nausea, vomiting, and gastritis. Tinnitus is one of the more specific complaints and is one of the best ways to identify the case, so as to answer the question: "Which of the following is the most likely diagnosis?"

Salicylates affect respiratory function in 2 ways:

- Directly stimulate the respiratory centers in the brainstem to cause a centrally mediated hyperventilation and hyperpnea
- Are directly toxic to the lungs themselves and can cause a noncardiogenic pulmonary edema similar to ARDS

Hyperthermia is possible. CNS toxicity such as confusion, coma, seizures, and encephalopathy can also occur, with possible death.

Salicylates also interfere with Krebs cycle and lead to a metabolic acidosis through the reversion to anaerobic glycolysis as a method of energy production in the body. In other words, salicylates lead to significant lactic acid production with metabolic acidosis and elevated anion gap. This ultimately results in a compensatory respiratory alkalosis.

The most specific test for diagnosis is **aspirin level**.

- Suggestive findings are **elevated anion gap with metabolic acidosis**. However, respiratory alkalosis may be the predominant defect, especially in early stages. Thus, blood gas can show low, high, or normal pH.
- Elevated prothrombin time and hypoglycemia may occur.
- Chest x-ray may be normal or show pulmonary edema.

Treatment. If the patient comes within 1 hour post-ingestion, attempt gastric decontamination. Charcoal may be useful, as it is in many types of ingestion. The mainstay of therapy, however, is increasing urinary excretion by alkalinizing the urine and administering aggressive

fluid resuscitation. When urinary pH rises, that will charge the salicylate molecule (a weak acid) and will block the reabsorption of the substance at the kidney tubule.

Dialysis is sometimes necessary. Indications for dialysis include:

- Renal failure
- CHF
- ARDS
- Persistent CNS symptoms (confusion/seizures)
- Hemodynamic instability
- Severe acid/base or electrolyte imbalance
- Hepatic failure with coagulopathy
- Salicylate level >100 mg/dL

Acetaminophen

> A 38-year-old man comes to the ED with complaints of vomiting and right upper quadrant pain. He explains that 4 days ago he ingested a full bottle (60 tablets) of acetaminophen (500 mg each). Bilirubin, AST, and prothrombin time are all elevated.

Acetaminophen is one of the few toxins about which precise toxicity levels are known; the ingestion of ~140 mg per kg is usually sufficient to cause serious toxicity. In other words, in an average-sized, 70-kg (154-lb) person, ~7–10 grams is enough to produce toxicity, and fatalities can occur >12–15 grams. In those with liver disease or concomitant alcohol abuse and thus depleted glutathione stores, the hepatotoxic dose is less (4 grams/day).

Clinical Presentation.

- **Stage I (first 12–24 hrs)**: nausea and vomiting, due to a gastritis caused by irritation from the pills
- **Stage II (24–72 hrs)**: asymptomatic period, as the acetaminophen is metabolized and part of the drug is converted to a toxic metabolite
  - At 24–48 hrs, subclinical elevation of the transaminases and bilirubin begins
  - At 48–72 hrs post-ingestion, clinically symptomatic signs of liver damage begin: more nausea, jaundice, abdominal pain, and signs of hepatic encephalopathy, renal failure, and death

Diagnosis. A clear history of a large volume of acetaminophen ingestion is initially sufficient to establish a diagnosis that warrants therapy with N-acetyl cysteine (NAC). Starting at 4 hours after ingestion, when most of the drug has been absorbed, drug levels are reliable. A nomogram based on relating the drug level to the time of ingestion is necessary to determine who will develop toxicity. In other words, a level by itself is not enough to determine who will

Note

Acetaminophen is rapidly and completely absorbed from the GI tract. Serum concentration can peak in 2 hours after oral ingestion at a therapeutic dose.

Note

Unlike most other cases of hepatitis, acetaminophen-induced hepatitis is acute in onset, progresses rapidly, is characterized by marked elevation of plasma aminotransferases (often >3,000 IU/L), and is associated with a rise in PT/INR.

develop toxicity. A certain level at 5–6 hours may not be toxic, but the same level at 10–12 hours post-ingestion may lead to the development of liver failure.

- Elevated AST is more common than elevated ALT. If a patient is known for alcohol abuse and presents with AST and ALT >1,000 U/L, the diagnosis is more likely to be acetaminophen toxicity than alcoholic hepatitis. Give NAC in such cases.
- Elevated bilirubin and prothrombin time indicate severe toxicity and hepatic necrosis. Studies show that NAC administration within the first 8 hours of severe drug poisoning improves liver microcirculation and prevents the need for liver transplant.

Note

NAC is now used for non-acetaminophen drug-induced liver injury, e.g., amoxicillin/clavulanate. It can be given IV or orally.

Treatment.

- NAC
  - Give within 8 hours of ingestion, when it is most effective
  - If >24 hours has elapsed, no specific therapy can reverse the toxicity (but still give NAC)
  - Avoid gastric emptying, as it would delay the administration of NAC as a specific antidote.
- Activated charcoal in repeated doses

Digoxin

Note

Arrhythmia is the most dangerous manifestation of digitalis poisoning.

Toxicity of digoxin is seen with suicide attempts and accidental therapeutic overdosage. Toxicity is more common with renal failure because 60% of digoxin is normally excreted renally, and it will accumulate.

The most common precipitating cause of digitalis toxicity is the reduction of potassium stores, often seen in patients with heart failure due to diuretic therapy or secondary hyperaldosteronism. **Hypokalemia** predisposes to toxicity because potassium and digoxin bind to the same site on the sodium–potassium ATPase pump, leading to increased intracellular calcium, thus leading to increased cardiac contractility. Drugs that have been implicated in digoxin toxicity include amiodarone, beta blockers, diltiazem, cyclosporine, macrolide antibiotics, indomethacin, spironolactone, and furosemide.

Clinical Presentation. GI symptoms are most common: nausea, vomiting, diarrhea, and anorexia. Neurologic and visual symptoms include blurred vision, color vision abnormality, hallucinations, and confusion. Cardiac disturbance is predominantly secondary to arrhythmia.

ECG abnormalities are common. Bradycardia, premature contractions, ventricular tachycardia, and any other arrhythmia may be seen (paroxysmal atrial tachycardia is most common). Hyperkalemia occurs acutely from inhibition of Na^+/K^+ ATPase by digoxin. Order a serum digoxin level if you suspect toxicity (due to history, etc.).

Treatment. For GI decontamination, give repeated doses of **charcoal**. For electrolyte abnormality correction, correct the **potassium**.

- Digoxin-specific antibodies (Digibind®) are useful for life-threatening toxicity, particularly with arrhythmias.
- Pacemaker placement may be necessary for bradycardia or third-degree AV block refractory to atropine.

Tricyclic Antidepressants

A 28-year-old man with a history of depression comes to the ED 1 hour after a suicide attempt with his tricyclic antidepressants and benzodiazepines. He is stuporous with respiratory rate 7/min. ECG shows a wide QRS. What is the next step?

Tricyclic antidepressants (TCAs) are characterized by a number of anticholinergic and sodium channel blocker side effects. This is the predominant cause of their cardiac and CNS toxicity.

Clinical Presentation.

- Anticholinergic-mediated findings (**most common**): dry mouth, tachycardia, dilated pupils, flushed skin
- Quick onset with rapid deterioration (common)
- Cardiac dysrhythmia with widening of the QRS complex (most serious side effect), leading to ventricular tachycardia and first-degree conduction blocks
- CNS effects: altered mental status, confusion, and seizure

Serum drug levels are the most specific test for diagnosis, but ECG with abnormalities is more important to determine who will have serious toxicity. ECG may be normal or show any range of ventricular or atrial arrhythmias or conduction delays.

Treatment. TCA overdose has anticholinergic side effects, which include impaired peristalsis and delayed gastric emptying. TCAs block sodium channels and can cause ventricular tachycardia.

- Charcoal in (first-line in the acute setting)
- Bicarbonate to protect the heart from the TCAs.
  - Give immediately if QRS >100 msec
  - Will not increase urinary excretion (as opposed to the treatment of aspirin overdose)

Anticholinergics

A 65-year-old man is brought to the ED by his wife with lethargy and confusion. She says that he has had a cold and has taken over-the-counter cold preparations for the last few days. On examination he is confused and does not recognize his wife. His temperature is 39.2 C (102.6 F), pulse is 130/min and blood pressure is 100/60 mm Hg. The skin is flushed, dry, and warm. The eyes are dilated.

Anticholinergic drugs competitively inhibit binding of the neurotransmitter acetylcholine to muscarinic acetylcholine receptors and are commonly called "antimuscarinic agents." Muscarinic receptors are found on peripheral postganglionic cholinergic nerves in smooth muscle (intestinal, bronchial, and cardiac), in secretory glands (salivary and sweat), on the ciliary body of the eye, and in the CNS. Anticholinergic agents do not antagonize the effects at nicotinic acetylcholine receptors, such as at the neuromuscular junction.

Overdose may occur in any age group with high dose, but most commonly presents in the elderly.

The onset of anticholinergic toxicity varies depending on the particular toxin, but usually occurs within 1–2 hours of oral ingestion. Some drugs may take up to 12 hours to have an effect. Be aware with patients on psychotropic agents.

The following medications may cause anticholinergic effects:

- Diphenhydramine
- Scopolamine and hyoscyamine
- TCAs
- Cyclobenzaprine
- Benztropine
- Belladonna

Clinical Presentation. Patients will present with the following characteristics:

- "Red as a beet": flushed, red skin due to cutaneous vasodilation
- "Dry as a bone": dry skin (anhydrosis) due to inability to sweat
- "Hot as a hair" anhidrotic hyperthermia
- "Blind as a bat": mydriasis
- "Mad as a hatter": delirium, psychosis, hallucinations, and seizures
- "Full as a flask": urinary retention and absent bowel sounds
- Tachycardia

Treatment is the ABCs, supportive care, and ECG monitoring.

- Sodium bicarbonate to stabilize the myocyte membrane and prevent ventricular tachycardia if there are prolonged QRS and QT intervals
- Benzodiazepines for possible seizure; do not use phenytoin or fosphenytoin

Note

The role of physostigmine as an antidote is controversial. It may be considered in moderate to severe toxicity. If used, the patient should be placed on a cardiac monitor and atropine should be readily available.

Note

With anticholinergic poisoning, do not use phenytoin or fosphenytoin for seizures that may occur.

Note

Remember **DUMBELSS** syndrome to recall the muscarinic effects:

- **D**efecation
- **U**rinary incontinence
- **M**uscle weakness/miosis
- **B**radycardia/bronchospasm
- **E**mesis
- **L**acrimation
- **S**alivation
- **S**eizure

POISONING

Organophosphate Poisoning

Organophosphates are chemicals used widely as insecticides/pesticides. They inhibit cholinesterase and have muscarinic and nicotinic effects. Patients tend to be farmers and gardeners.

- **Nicotinic effects**: weakness and decreased respiratory drive
- **Muscarinic effects**: defecation, urinary incontinence, muscle weakness/miosis, bradycardia/bronchospasm, emesis, lacrimation, salivation, seizure

To diagnose, check RBC cholinesterase levels. Do not delay treatment while waiting for results.

Treatment. The first step is for the physician to put on protective clothing, as organophosphates are absorbed by the skin. Then, have patient remove clothing immediately. Start atropine immediately to treat the bradycardia. Start pralidoxime (2-PAM), which restores cholinesterase activity and reverses both the nicotinic and muscarinic effects.

Toxic Alcohol Poisoning

All of the toxic alcohols—methanol, ethylene glycol, ethanol, and isopropyl alcohol—can produce intoxication. They are found in many household and commercial settings.

Methanol and ethylene glycol are metabolized by alcohol dehydrogenase.

- **Methanol** (wood alcohol) is found in paint thinner, photocopier fluid, solvents, and windshield washer solution.
  - Metabolized to formaldehyde and formic acid
- **Ethylene glycol** is found in automotive antifreeze.
  - Metabolized partially to oxalic acid and oxalate, which leads to kidney damage

Clinical Presentation.

- **Methanol ingestion**: visual disturbances (even blindness), due to the production of formic acid
- **Ethylene glycol ingestion**: renal failure, oxalate crystals, and stones in the urine
- **Isopropyl alcohol ingestion**: distinguished only after a specific drug level is done by the history or after acidosis has developed in the absence of an elevated anion gap

Diagnosis. Determining specific levels of each alcohol is the most specific test.

- **Methanol and ethylene glycol**: increased serum osmolar gap and metabolic acidosis with elevated anion gap
- **Ethylene glycol**: oxalate crystals in the urine, increased BUN/creatinine, or urine fluorescence (add fluorescein to the urine and observe with ultraviolet Wood's lamp); possible hypocalcemia
- **Isopropyl alcohol**: increased serum osmolar gap without an elevated anion gap

Treatment.

- Fomepizole (alcohol dehydrogenase inhibitor) (**drug of choice**) to inhibit the production of toxic metabolites without leading to intoxication
- Dialysis for those with severe anion gap metabolic acidosis or signs of end-organ damage (coma, seizures, renal failure)

Note

Methanol, ethylene glycol, and isopropyl alcohol ingestion will all result in an osmolar gap., usually >25 mOsm.

Note

Charcoal will not inhibit the absorption of alcohols. Do not use.

Note

In the past, methanol and ethylene glycol intoxication were treated with ethanol infusion (to prevent the production of the toxic metabolites), followed by hemodialysis to remove the substance from the body.

Carbon Monoxide Poisoning

> You are the chief resident at a metropolitan training program at the time of a fire at a large office building. A total of 2,500 people come to the ED for treatment of smoke inhalation. Among them is a 68-year-old man with a history of aortic stenosis who had to walk down 90 flights of stairs.

Note

In Northern climates, space heaters during wintertime are a common cause of carbon monoxide poisoning. The most common symptom is headache, along with nausea.

Poisoning with carbon monoxide (CO) occurs by exposure to burning materials (gasoline, wood, natural gas) and by entrapment in fires and smoke inhalation. CO itself is odorless and tasteless. CO poisoning is common, potentially fatal, and underdiagnosed because of its non-specific clinical presentation.

Note

Low levels of CO poisoning are present in most tobacco smokers.

- CO binds to hemoglobin 200× more avidly than oxygen.
- Carboxyhemoglobin decreases release of oxygen to tissues and inhibits mitochondria, resulting in tissue hypoxia and anaerobic metabolism (similar to what would occur with anemia).

Clinical Presentation.

- Pulmonary symptoms include dyspnea, tachypnea, and shortness of breath.
- Cardiac symptoms include chest pain, arrhythmia, and hypotension.
- Early neurologic symptoms include headache (most common), nausea, blurry vision, and dizziness, while late symptoms include confusion, seizures, impaired judgment, and syncope.

Note

There are some similarities to the initial presentations of CO poisoning and hypoglycemia. If fingerstick glucose is normal, that should raise your suspicions.

Carboxyhemoglobin (COHb) levels indicate the severity of the exposure.

- **COHb level <10%** may occur in city dwellers who are smokers
- **COHb level 20–30%** mild symptoms
- **COHb level 30–50%** moderate to severe symptoms
- **COHb level >50–60%** may be fatal

Carbon monoxide pulse oximetry (a co-oximeter) is the initial diagnostic test for suspected CO poisoning, as it provides a way to measure carboxyhemoglobin. Routine pulse oximetry is not helpful.

Influenza is the most common misdiagnosis because most people present during wintertime. When an entire family presents with "flu" symptoms without fever, think CO poisoning.

- Arterial or venous blood gases: metabolic acidosis is present from the failure of carboxyhemoglobin to release oxygen to tissues; pO2 will be normal
- CPK may be elevated.

Treatment.

- Remove the source of exposure and give 100% oxygen
- For severe cases, give hyperbaric oxygen
  - COHb >25% (pregnant women >15%)
  - Myocardial ischemia
  - ECG changes
  - CNS abnormalities other than headache or chest pain

In room air, carbon monoxide has a half-life of 4–6 hours. On 100% oxygen, it decreases to 40–80 minutes. On hyperbaric oxygen, it decreases to 15–30 minutes.

Corrosives

The oral ingestion, inhalation, or cutaneous/ocular contact with corrosive substances is commonly seen in emergency medicine, especially with children.

- The most common household **acids** are toilet bowl cleaners, drain openers, swimming pool chemicals, and metal cleaner.
- The most common **alkali** ingestions are from dishwasher detergent, hair relaxer, and oven cleaner.

In most circumstances, **alkali exposures are more serious than acid exposures**, since alkaline substances are more destructive to tissues.

Symptoms from ingestion injury include the following:

- Oral pain
- Drooling
- Odynophagia
- Abdominal pain
- Possible esophageal injury with subsequent stricture formation (from acid or alkali ingestion)
- Possible gastric perforation

The history of exposure with subsequent characteristic injury is sufficient to establish the diagnosis. Upper endoscopy is critical for determining the extent of the injury.

Treatment.

- Wash out the mouth immediately with large volumes of cold water.
- Irrigate ocular exposures with large volumes of saline or water, followed by fluorescein staining to determine if there is significant corneal injury.
- Do not induce emesis with acid or alkaline ingestion because it can worsen the injury. Simply give water.
- Do not try to neutralize the acid with a base or a base with an acid because a heat-producing reaction can occur, which would destroy more tissue.
- Charcoal is not useful, nor are steroids or prophylactic antibiotics.

Lead Poisoning

Up to 12 million preschool children per year may be affected by lead in the United States. Lead is ingested from paint, soil, dust, drinking water, and in the past from gasoline. Lead poisoning is primarily a chronic condition, not acute.

- Can be absorbed by inhalation, from the skin, or from the GI tract (increased by deficiencies of zinc, iron, and calcium)
- Is primarily excreted through urine (80–90%), with the remainder through stool

Note

Corrosive describes a chemical that will dissolve the structure of an object (can be acids or bases). In other words, when it comes into contact with a surface, the surface will deteriorate.

Caustic is sometimes used as a synonym for corrosive but really only refers to strong bases, not acids.

Note

The most common serious injury is the oral ingestion of liquid drain cleaner.

Note

Corrosives/caustics are immediately dangerous to tissues they contact, while **poisons** may have systemic effects which require time to be evident.

Note

Lead is primarily excreted in urine and bile.

Clinical Presentation

- Adults: abdominal pain, anemia, renal disease, azotemia, neurologic manifestations such as headache and memory loss; possible hypertension
- Children:
  - Acute: abdominal pain, anemia, lethargy, seizures, coma
  - Chronic: irreversible neurologic damage such as mental retardation and poor cognitive/behavioral function

Blood lead level is the key to diagnosis, with **<10 µg/dL** considered acceptable. In children, "lead lines" are densities seen at the metaphyseal plate of the long bones, indicating long-term exposure.

Note

Think **lead** in patients who have both microcytic anemia and abdominal pain.

Treatment. Treatment includes chelation with calcium EDTA, dimercaprol (BAL), penicillamine, or succimer (oral therapy). Urine output should be maintained at 1–2 mL/kg/hr to aid in maximal excretion.

Management of lead toxicity/poisoning should be done according to blood lead level:

- **Mild (5–44 mcg/dL):** no treatment needed; repeat level in 1 month
- **Moderate (45–69 mcg/dL):** 2,3 dimercaptosuccinic acid (DMSA)
- **Severe (≥70 mcg/dL):** DMSA + EDTA (calcium disodium edetate)

ALCOHOLISM

A 35-year-old man is brought to the ED by his wife after he had a seizure. He is agitated and combative. He is yelling and trying to hit the nurses, and tells you that he is in France. He is also yelling at his mother, who is not in the room. His wife tells you that he drinks a liter of whiskey a day, though he has not had any in the last few days because he didn't have the money. His pulse is 130/min, blood pressure 160/90 mm Hg, and respirations 24/min. He is diaphoretic and extremely irritable. His temperature is 38 C (100.4 F). The rest of the exam is unremarkable.

Alcoholics may present with any one of the following symptoms:

Note

The diagnosis of all alcohol withdrawal–related syndromes is made clinically, not by lab values.

Mild withdrawal: tremors, tachycardia, anxiety; seizures may be seen 6–12 hours after last drink

Delirium tremens (DT) (manifests 48–72 hours after last drink but can last up to 10 days): mental confusion, autonomic hyperactivity, visual hallucinations, severe agitation, diaphoresis

Alcoholic hallucinosis (may be confused with DT) (starts 12–24 hours after last drink but can last days to weeks)

- Paranoid psychosis without tremors and confusion
- Normal vital signs (no hypertension or tachycardia)

- No agitation
- Normal appearance except for auditory (most common), visual, or tactile hallucinations

Wernicke encephalopathy: confusion, ataxia, and ophthalmoplegia (nystagmus)

Korsakoff psychosis: amnesia and confabulations

Treatment. Alcohol withdrawal has a very high mortality rate (5%). Benzodiazepines can be life-saving (**taper dose slowly**). Diazepam and chlordiazepoxide are common, due to their long half-life. Hydrate with isotonic fluids and electrolyte replacement.

- Anticonvulsants have no role.
- Avoid antipsychotics such as haloperidol, as they can lower the seizure threshold and cause prolonged QT interval.

Symptom-triggered therapy is recommended. A work-up for alternative diagnosis is also very important.

- Be careful when using benzodiazepines for cirrhosis
- CT head to look for intracranial bleed
- Lumbar puncture to rule out meningitis if there is a fever
- Chest x-ray: look for aspiration pneumonia
- High doses of thiamine IV for Wernicke and Korsakoff; treatment for alcoholic hallucinosis is benzodiazepines and haloperidol (there is no risk of seizures, so it can be used here)

Clinical Recall

A 17-year-old woman who drank from her grandfather's whiskey bottle is brought to the ED with intermittent blurring of vision and vomiting. Which of the following is the treatment of choice?

A. Activated charcoal

B. Ethanol

C. Fomepizole

D. Thiamine

Answer: C

HEAD TRAUMA

A 20-year-old man is playing football when he is struck in the head and loses consciousness for a few minutes. He awakens and has some motor weakness of his left arm, which seems to slowly worsen over the course of the next hour as he is brought to the ED.

Note

Benzodiazepines are dosed and administered using a validated assessment tool, the most common of which is Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar) scale. This requires formally assessing the patient at regular intervals.

Head trauma is any degree of traumatic brain injury resulting in a range of injuries, from scalp laceration to headache to loss of consciousness or focal neurologic deficits. The term does not imply a specific mechanism of injury. The injury can result in concussion, contusion, epidural hematoma, subdural hematoma, or traumatic subarachnoid hemorrhage. Cerebral contusion can progress to intraparenchymal hemorrhage.

Clinical presentation is often only suggestive of the degree of injury. The specific injury can only be determined with CT scan.

- All forms of head trauma can result in headache, amnesia, and loss of consciousness. The degree of amnesia is loosely associated with the degree of head trauma, i.e., the worse the trauma, the more memory one loses.
- Memory loss starts from the time of injury and stretches both forward (**anterograde**, in which one doesn't remember events since the time of the injury) and backward (**retrograde**, in which one forgets past events).
  - Retrograde amnesia (more common) starts from the time of the injury and moves further back in time depending on the severity of the injury. The more severe the injury, the further back in time you forget.
  - Recovery of memory starts with recollection of the most distant progressing to the most recent memories.
- Loss of consciousness, although possible in any form of head trauma, is not always present, even with relatively severe forms of brain injury. There can be very severe intracranial bleeding (e.g., subdural hematoma) without a loss of consciousness. This is particularly true of chronic subdural hematoma.
- Concussion is generally not associated with focal neurologic findings, such as motor or sensory deficits. The presence of focal findings, starting in order of highest frequency, is most commonly associated with epidural and subdural hematomas and contusion.

Diagnosis. CT scan of the head is the mainstay of diagnosis of brain injury. Contrast enhancement is not necessary because blood does not enhance with contrast.

- Hemorrhage should be visible instantly if present at the time of the initial presentation.
- **Subdural hematoma is crescent-shaped** and **epidural hematoma is lens-shaped**.

Follow-up scanning is also done with CT, as needed.

- Skull x-ray is never used for diagnostic purposes.
- Normal x-ray does not exclude hemorrhage, and abnormal x-ray does not confirm the presence of a hemorrhage.
- Cervical spine x-rays should be obtained if there are focal findings consistent with cervical radiculopathy or if spinal tenderness is present. Even without these findings, you should have a very low threshold for obtaining cervical spine x-rays.

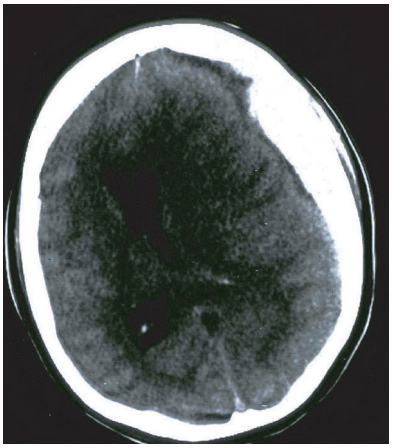


Figure 10-15. Subdural Hematoma

(venous in origin; may be acute or chronic and may or may not result in midline shift)

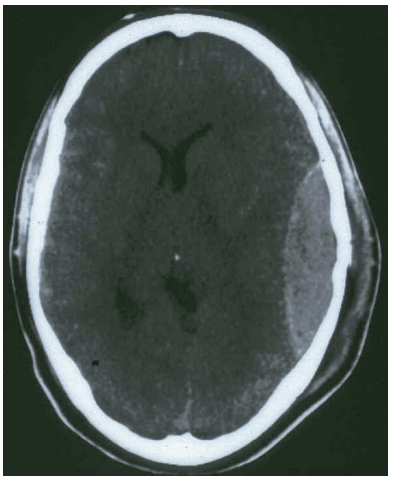


Figure 10-16. Epidural Hematoma

(usually arterial and associated with skull fractures)

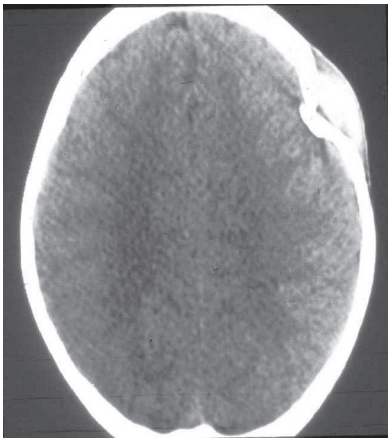


Figure 10-17. Depressed Skull Fracture

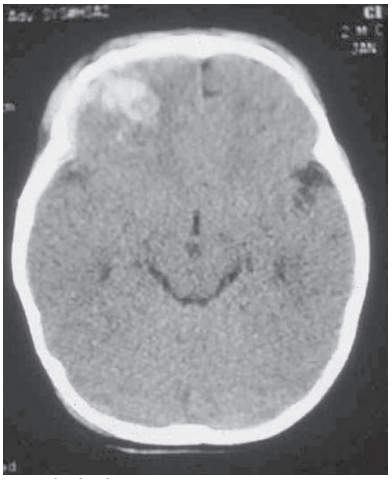
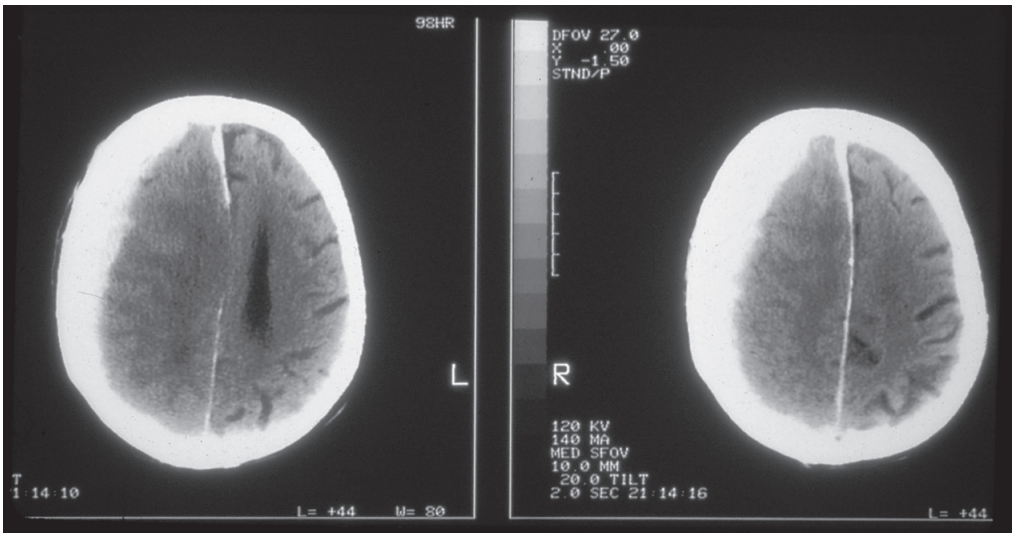


Figure 10-18. Cerebral Contusion

(petechial hemorrhage and/or edema, which may worsen over days)

Note

A concussion is diagnosed by a history of loss of consciousness plus a negative CT scan of the head.



Dr. Conrad Fischer

Figure 10-19. CT Scan Demonstrating Subdural Hematoma with a Midline Shift

Treatment. Severe intracranial hemorrhage should be managed by lowering the intracranial pressure.

- For acute response, use hyperventilation to pCO_2 of 30–35, which will cause vasoconstriction of cerebral vessels and then a drop in intracranial pressure; use in moderation and for limited amount of time.
- Osmotic diuretics such as mannitol and elevation of the head of the bed are also helpful for lowering intracranial pressure. This is in preparation for surgical evacuation. Elevate the head of the bed to 30 degrees and maintain systolic BP to 110–160 mm Hg. This slight degree of hypertension assures that the cerebral perfusion pressure is adequate.
- Steroids are not effective for head trauma.

Cerebral perfusion pressure is best when mean arterial pressure ≥60 mm Hg above the intracranial pressure. Stress ulcer prophylaxis with medications such as PPIs and H2 blocker is given after all severe head trauma and after intubation for >72 hours.

Subarachnoid Hemorrhage

A 52-year-old woman is at her office when she develops the sudden onset of a severe headache, stiff neck, photophobia, and loss of consciousness. She awakens within the hour that she arrived in the hospital. She is noted to have a severe headache, nuchal rigidity, photophobia, and temperature 38.5 C (101.3 F).

Subarachnoid hemorrhage (SAH) is the sudden onset of bleeding into the subarachnoid space. It most often occurs spontaneously.

- Aneurysm formation is the most common etiology. The aneurysms can be saccular or fusiform, and are most commonly around the circle of Willis. The most common sites are anterior communicating artery, middle cerebral artery, and posterior communicating artery.
- There is an association with polycystic kidney disease, Ehlers-Danlos syndrome, and some other connective tissue diseases.
- Head trauma is rarely a cause.

Clinical Presentation. Sudden onset of severe headache is the hallmark of SAH. Other features include:

- Loss of consciousness due to sudden rise in intracranial pressure (up to 50% of patients)
- Focal neurologic symptoms (>30%), most commonly from compression of the oculomotor cranial nerve
- Other possible neurologic defects, due to the pressure of the bleed dissecting into surrounding tissues
- Nuchal rigidity, photophobia, headache, and papilledema due to meningeal irritation
- Fever 3–4 days after the initial hemorrhage; this can simulate meningitis because SAH is a form of chemical meningitis from irritation by the blood
- Seizures (extremely common); 1-year mortality can be up to 50%, with half of the patients dying upon immediate occurrence of the bleed

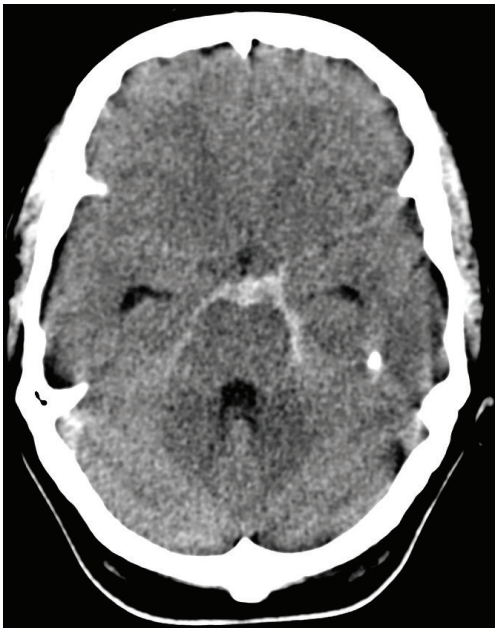


Figure 10-20. Subarachnoid Hemorrhage on CT Scan

Note

A spinal headache may occur after a lumbar puncture in some patients. This is treated with a blood patch.

Clinical Pearl

Traumatic lumbar puncture may cause RBC in the CSF, but xanthochromia is absent.

Longer-term manifestations include the development of focal deficits, seizures, rebleeding, and hydrocephalus. Vasospasm after the bleed results in hypoperfusion to portions of the brain parenchyma and the development of stroke. Rebleeding occurs when the clot falls off of the original site of bleeding. Up to half of the people who rebleed will die. Hydrocephalus occurs when the blood cells clog up the arachnoid granulations through which CSF normally drains.

Diagnosis. The initial test is the CT scan, which is more sensitive than MRI for the diagnosis of SAH. The CT, done without contrast, has a sensitivity of 90–95% within the first 24 hours after the onset of the bleed. With time, the diagnostic sensitivity of the CT actually diminishes, as the red cells within the CSF hemolyze and are resorbed and converted into the yellowish coloring (described on CSF examination as **xanthochromia**).

- If the initial CT is normal and SAH is still suspected, do a **lumbar puncture**. The lumbar puncture is the most sensitive diagnostic test, i.e., an absence of red cells and xanthochromia on lumbar puncture essentially excludes an SAH. Xanthochromia is due to lysis of RBCs and formation of bilirubin (straw-colored CSF). Xanthochromia needs 4–6 hours to develop.
- Angiography is used to determine the specific anatomic site of the vascular defect and the site of the bleed. ECG abnormalities such as inverted or enlarged T-waves are often associated with the development of SAH and are not a cause for alarm.

Treatment. Initial steps are to maintain systolic BP at 110–160 mm Hg. Pressure higher than that can provoke more bleeding, while pressure lower can provoke cerebral ischemia through hypoperfusion (given the increased intracranial pressure).

- Use nimodipine, a calcium-channel antagonist, to lower the risk of spasm in the blood vessel, thus lowering the risk of subsequent stroke.
- Do **angiography** to determine the anatomic site that will need catheter or surgical correction. It is important to perform this so that surgical correction (usually with embolization or clipping of the AVM) can occur before rebleeding develops. If hydrocephalus occurs, then shunting will be needed. Embolization is superior to surgical clipping.

BURNS AND RADIATION INJURY

Burns

> A 32-year-old fireman is caught in a fire and briefly trapped under a burning staircase. He is quickly extracted and brought to the ED fully alert. His respiratory rate is 14/min and weight is 220 pounds. There is soot in his mouth and nose and on his face, and his sputum is not carbonaceous. The nasal hairs are singed. He has no stridor or hoarseness, and the lungs are clear to auscultation. He has first-degree burns on his right leg and second- and third-degree burns on his right arm and chest.

Injury due to burns can be divided into several types. The most common causes of death from fire are **smoke inhalation** and **carbon monoxide poisoning**. Thermal injury is most dangerous when it is respiratory related.

Skin injury is labeled *first-degree* when the skin is fully intact, even though it may be discolored.

- **First-degree** burns are not associated with blister formation and appear "sunburn-like." The skin may be red or gray, but capillary refill remains normal.
- **Second-degree** burns result in blister formation.
- **Third-degree** burns are deeper and destroy skin appendages such as sweat glands, hair follicles, and sometimes pain receptors. This leaves patients with third-degree burns insensate; any pain they perceive is from surrounding structures where pain receptors are intact.

Although not apparent at first, respiratory injury can be the most life-threatening injury.

- Soot in the mouth or nose, stridor, wheezing, altered mental status, burned nasal hairs, and burns involving closed spaces are all clues to impending pulmonary and laryngeal edema.
- Shock occurs not only from direct skin loss but also from release of a host of mediators that cause **diffuse capillary leak** for the first 18–24 hours. Serious capillary leak occurs when the percentage of serious body surface area burn >20–25%.

Clinical Presentation. Altered mental status, dyspnea, headache, and chest pain are clues to severe carbon monoxide poisoning. Laryngeal edema can result in stridor, hoarseness, and dyspnea. Soot in the nose and mouth can imply impending airway compromise.

The "**Rule of Nines**" is used to determine the body surface area that has been burned, and thus assess fluid resuscitation needs:

- **Head and arms**: 9% each
- **Chest, back, and legs**: 18% each
- Patchy burns can be estimated by using one hand's width as an estimate of 1% of body surface area burned.
- Circumferential burns are critical in the assessment because as they heal, they tighten and cut off circulation, leading to limb compromise and the need for escharotomy.

Diagnosis. Besides the obvious burn, carboxyhemoglobin levels are essential in severe burns. Severe burns are defined as combined second- and third-degree burns >20% in adults, or >10% in the very old or very young, or third-degree burns >5% of body surface area (BSA). Chest x-ray and bronchoscopy help determine the exact extent of respiratory injury when it is uncertain. Bronchoscopy can reveal severe thermal injury to the lungs even when the initial chest film is normal. Foley catheter placement helps determine the adequacy of fluid resuscitation.

Treatment.

- If patient has signs of severe respiratory injury, the first step is to intubate before more severe laryngeal edema can occur and make the intubation difficult.
- If carboxyhemoglobin level is significantly elevated (>5–10%), administer 100% oxygen.
- Fluid resuscitation over the first 24 hours is based on a formula of 4 mL per % BSA burned per kg. Use second- and third- degree burns in your calculation.
  - Use Ringer's lactate as the preferred fluid; give 50% of the fluid in the first 8 hours, 25% in the second 8 hours, and 25% in the final 8 hours. (This is known as the **Parkland formula**.)
  - Afterward, when the diffuse capillary leak improves, give enough fluid to maintain urine output >0.5–1 mL per kg per hour.

Note

The **Rule of Nines** differs between adults and children. Refer to the Pediatrics book for more information on burns in children.

- Give stress ulcer prophylaxis with H2 blocker or PPI.
- To prevent infection, use topical treatment with silver sulfadiazine.
- Do not break blisters and do not use steroids.
- Escharotomy is useful in circumferential burns.
- Skin grafting is done on the basis of the size and severity of the injury.
- Patients with burn injuries are at increased risk for pseudomonal and staphylococcal infections; if there is concern for infection, give IV antibiotics that cover these organisms.

Radiation Injury

- **Ionizing radiation** damages tissues primarily through destructive changes to DNA molecules. Ionizing radiation is lethal and can often cause cancer. Longer exposures give worse injury.
- **Nonionizing radiation** is less destructive to tissue and causes injury primarily as burns. Examples include infrared, ultraviolet, and microwave radiation.

Clinical Presentation. To give a sense of scale, mortality is almost zero with <2 Gy (or Sv) of exposure. This rises almost to 100% mortality with >10 Gy (or Sv). (10 Gy = 1,000 rad.)

Any cell can be damaged by ionizing radiation, but the more rapidly the cell divides, the more vulnerable it is to radiation. This is because more DNA damage can be done during the time of division.

Common sites of radiation injury include the following:

- **Bone marrow**: As little as 2–3 Gy (200–300 rad) can depress lymphocyte count. Neutrophils are the next most sensitive cell, while erythrocytes are the least sensitive.
  - Leukemia (**earliest and most common cause of cancer from radiation exposure**)
  - Thrombocytopenia, with possible death from bleeding
  - Infection and bleeding from depressed bone marrow function (**most common causes of death in acute exposure**)
- **Gonads**: 2–3 grays result in temporary aspermatogenesis, while 4–5 grays can make men permanently sterile. Testes are more sensitive than ovaries.
- **GI**: Nausea and vomiting are the most common early symptoms of radiation exposure (50% of cases with 2 Gy [200 rad] exposure and 100% of patients with >3 Gy exposure). Also, the rapidly reproducing intestinal lining ulcerates, leading to bleeding and infection later.
- **Other common sites of radiation injury**: the skin, salivary glands, respiratory epithelium, and thyroid glands

Treatment. Management is supportive. There is no specific therapy to reverse radiation injury.

- Antiemetics, given that nausea is such a common feature of radiation sickness
- Blood products, i.e., platelets and RBC transfusions; WBC transfusions do not help
- Colony-stimulating factors (G-CSF, GM-CSF) to help restore marrow function
- Antibiotics, used as needed when infection develops
- Bone marrow transplantation (occasionally useful)

THERMOREGULATORY DISORDERS

Heat Disorders

Heat disorders are classified as exertional disorders, common in younger individuals doing strenuous activity ("exertion") in hot environments, or nonexertional disorders, common in the elderly, the very young, and the chronically ill.

Exertional disorders

- **Heat cramps** (mild exertional disorder) can happen to any healthy person who develops fluid and electrolyte depletion
  - Patient develops painful muscular contractions lasting a few minutes, with muscle tenderness present. Body temperature is normal.
  - Patient is able to sweat. There are no neurologic abnormalities.
  - Treatment is rest, oral rehydration, and salt replacement.
- **Heat exhaustion** (more severe)
  - Patient is weaker with more systemic symptoms. Body temperature may be slightly elevated.
  - Patient is able to sweat and remove heat from the body. There may be mild neurologic symptoms such as headache, nausea, and anxiety, but severe confusion is rare.
  - Death is very unlikely, but the disorder can progress to heat stroke if not treated.
  - Treatment is oral fluid and electrolyte replacement. For severe weakness, IV hydration may be needed.
- **Heat stroke** (very severe and potentially life-threatening)
  - Patient has lost the ability to remove heat from the body because of an impaired ability to sweat; 50% of patients retain some capacity to sweat but in insufficient amounts to keep up with heat generation.
  - Body temperature may become severely elevated (>41C), resulting in confusion, disorientation, nausea, blurred vision, and seizures.
  - Numerous lab abnormalities may occur, including hemoconcentration, rhabdomyolysis, and elevated BUN, creatinine, and white cell count.
  - Anuria, DIC, and lactic acidosis may develop.
  - Treatment for **non-exertional heat stroke** is IV fluid replacement and external evaporative cooling of the body (place in cool environment and spray with water, then fan to evaporate the fluid). Treatment for young athletes with **exertional heat stroke** is immersion in ice water. In the elderly, chlorpromazine and diazepam can be used to control shivering.

Nonexertional disorders

- **Malignant hyperthermia** occurs as an idiosyncratic reaction to an anesthetic such as halothane or succinylcholine. Virtually any anesthetic may cause it.
  - Rhabdomyolysis may develop.
  - Treatment is dantrolene, which directly relaxes muscles by inhibiting calcium release from the sarcoplasmic reticulum,

- **Neuroleptic malignant syndrome** occurs an idiosyncratic reaction to a phenothiazine or butyrophenone such as haloperidol. It is postulated that dopamine blockade or depletion can lead to abnormal regulation of body temperature and Parkinsonian features.
  - Muscular rigidity and rhabdomyolysis may occur; also, altered mental status, muscle rigidity, and autonomic dysfunction
  - Treatment, besides stopping the drug, is bromocriptine and dantrolene.
- **Serotonin syndrome** (common and potentially life-threatening) is a drug reaction that often occurs when 2 medications affecting the body's level of serotonin are taken together, such as SSRI, SNRI, meperidine, and tramadol.
  - Symptoms can range from mild to severe: agitation, confusion, muscle rigidity, and heavy sweating
  - No single test can confirm serotonin syndrome, and a number of other conditions have similar symptoms
  - Treatment is supportive care and cyproheptadine (serotonin antagonis)

Hypothermia

Hypothermia is a medical emergency that occurs when the body loses heat faster than it can produce heat, causing a dangerously low core body temperature <35 C (<95 F) (normal 37 C or 98.6 F). Core temperature is measured with a rectal probe or through the esophagus. It is often seen with alcohol intoxication, particularly in the elderly.

Severe hypothermia is core temperature <30 C (<86 F).

Clinical Presentation. Symptoms of severe hypothermia commonly relate to the CNS. Lethargy, confusion, and weakness may occur. Death is most commonly a result of arrhythmia (Osborne wave or J-wave), from the effect of the cold on altering cardiac conduction. Other complications include metabolic acidosis, respiratory acidosis, kidney injury, and hyperkalemia.

Note

Hypothermia must be worked up for precipitant factors:

- Hypoglycemia (most common cause)
- Hypothyroidism
- Sepsis

Diagnosis. The ECG can show a wide variety of serious arrhythmias, including ventricular fibrillation or ventricular tachycardia. The most characteristic finding is an elevated J-point, known as Osborne waves. J-wave elevation may mimic ST-segment elevation.

Treatment. Most patients respond well to common-sense treatment such as a warm bed, bath, and heated blanket. For very severe cases, use warmed IV fluid or humidified oxygen. Use caution, though, because overly rapid rewarming can cause arrhythmias; if life-threatening arrhythmias occur, it is important to continue resuscitative efforts until body temperature **>35 C (>95 F)**. If the patient is cold but not shivering, active measures should be used:

- **Active external rewarming**: only to truncal areas; warm blankets; heat lamps; hot-water bottles
- **Active internal rewarming**: warm IVFs (45 C [113 F]), warm humidified oxygen (45 C [113 F]), warmed gastric lavage via NGT, warmed hemodialysis

Hypothermia is one of the few times in which **a patient can be resuscitated from pulselessness beyond the usual 10 minutes of efforts**.

Clinical Recall

A 65-year-old woman is brought to the ED after a fall in the shower. On examination, there is a contusion on the posterior aspect of the skull. On examination of the eye, there is mild dilation of the right pupil with evidence of papilledema in both eyes. Which of the following would not be considered in the management of this condition at this time?

A. Administer IV steroids

B. Elevate head end of bed

C. Hyperventilate the patient

D. Maintain systolic blood pressure >110 mm Hg

E. Mannitol infusion

Answer: A

DROWNING

Drowning is a significant worldwide public health concern. It is a major cause of disability and death, particularly in children. At least 35% of survivors sustain moderate-to-severe neurologic sequelae.

- Alcohol and drug use are strongly associated with an increased risk of death by drowning.
- Muscular exhaustion, head and spinal trauma, or acute myocardial infarction are predispositions to drowning and near drowning.
- 10–20% of drowning victims may have suffered dry drowning, in that there is no water aspirated into the lungs. Dry drowning is secondary to laryngospasm.

Drowning from aspiration of water can be divided into 2 types:

- **Freshwater** (hypotonic) alters pulmonary surfactant, resulting in unstable alveoli which then collapse.
  - The hypotonic water is absorbed into the body, leading to **acute hypervolemia, hemodilution, and intravascular hemolysis.**
  - At autopsy, the lungs may contain little water.
- **Seawater** (hypertonic) draws water out of the body into the lung, causing **systemic hypovolemia and hemoconcentration**.
  - The lungs become even more heavy and fluid-filled because the surfactant is essentially washed out.

Presentation. Only the presentation of near drowning is important to discuss because drowned victims are dead. Presentation can vary from coma to agitation. Cyanosis, coughing, and signs of pulmonary edema, such as tachypnea, tachycardia, and blood-tinged sputum are common. Rales and rhonchi can be found on the exam. Hypothermia is also common.

Note

Near drowning is survival after immersion, at least for some time. Morbidity is high and death may occur later. The exact definition is still the topic of much debate.

Drowning is defined as death within 24 hours after submersion in water.

Note

Young children are more likely to drown in freshwater (e.g., swimming pool) than in seawater.

Laboratory Findings. Arterial blood gases show hypoxia and hypercarbia, as well as metabolic acidosis from anaerobic metabolism. Hyperkalemia may be present if there is significant hemolysis. Renal insufficiency on the basis of hypoxia is a rare finding.

Treatment. The first task is to remove the patient from the water and do ABCs (airway/breathing/circulation) of resuscitation.

- Endotracheal intubation as needed
- Supplemental oxygen

After removal from water, the most important initial step is to **establish an adequate airway**. Continuous positive airway pressure (CPAP) is the most effective treatment and gives the best correction of hypoxia and acidosis. Even if the patient appears comfortable initially, observe for 24 hours because ARDS (acute respiratory distress syndrome) may develop as a late finding.

The following treatments **do not help and may be harmful**:

- **Abdominal thrusts** may lead to aspiration of gastric contents.
- **Antibiotics** are indicated only if pneumonia develops.
- **Steroids** have no benefit.

ALLERGIC REACTIONS

Anaphylaxis

Anaphylaxis is a syndrome of histaminergic release in which there are signs of severe injury such as urticaria, angioedema, hypotension, tachycardia, and respiratory compromise. As an idiosyncratic reaction, patients can develop anaphylaxis from any medication, food, insect bite, or antigenic substance entering the body by oral or parenteral route.

- Penicillin, phenytoin, contrast agents, and allopurinol allergy are common.
- Chocolate, peanuts, and strawberries are common.
- Bee stings are common.

Clinical Presentation. Mild symptoms include a rash known as "hives." More severe symptoms include dyspnea, stridor, tachycardia, hypotension, and hemodynamic collapse.

Treatment. Treatment is epinephrine (intramuscular or IV) and inhaled albuterol.

Note

Antihistamines and **corticosteroids** have not been proven to improve outcomes in anaphylaxis (and neither agent would work quickly enough). **Steroids** are sometimes given to prevent a delayed recurrence of symptoms, but this is not supported by strong evidence.

Venomous Bites and Stings

Cat and dog bites

Dog bites (most common bites in United States) are usually ripping and tearing in nature, whereas cat bites are usually a puncture wound.

Clinical Presentation. Infection is more likely in patients with a delay in treatment, extremes of age and extremity injuries. Infections are most often polymicrobial.

- Cat bites are highly associated with *Pasteurella multocida*.
- Dog bites are associated with *Pasteurella, Eikenella*, hemolytic streptococci, *Staph aureus*, and *Capnocytophaga canimorsus*.

Treatment. Treatment is exploration, debridement, irrigation, and proper wound care. If prophylactic antibiotics are indicated, the drug of choice is amoxicillin and clavulanate (with penicillin-allergy, use a combination of clindamycin or metronidazole plus ciprofloxacin or trimethoprim/sulfamethoxazole or doxycycline).

Indications for antibiotic prophylaxis:

- Any cat bite
- Any bite on hand, face, joint, or genitals
- Immunocompromised status
- Asplenic patient (high risk of overwhelming sepsis from *Capnocytophaga canimorsus*)

Most wounds should be left unsutured except for facial wounds for cosmetic reasons. Never suture the hand.

Human bites

Human bites can occur as a result of incidental or purposeful injury. They carry an infection rate of 15%, which is greater than cat and dog bites together. The most common organisms are anaerobic and aerobic bacteria, specifically, *Eikenella corrodens*. Hepatitis B and HIV can also be transmitted through bites but are much less common.

Treatment. Clean and irrigate wound well. If bite <12 hours old, close loosely.

- Tetanus, hepatitis B, and prophylaxis counseling
- 5–7 day course of prophylactic antibiotics
- There is no place for cultures on fresh bites.

Note

All human and monkey bites should receive prophylactic antibiotics.

Rabies

Rabies (bite) is a viral disease that affects the CNS. It is carried by bats, dogs, bats, raccoons, rats, skunks, and foxes; transmission occurs through their **saliva** a few days before death, when the animal "sheds" the virus. Since it affects the nervous system, most rabid animals behave abnormally.

The incubation period of rabies is up to 1 year. It is nearly 100% fatal once the disease has been contracted.

Clinical Presentation. Prodrome of 2–10 days, including fever and paresthesias at the bite site. Neurologic changes include aphasia, paralysis, hypersalivation, and myoclonus. Diagnose with viral cultures from saliva, CSF, or serum.

Treatment. Ribavirin has been used in confirmed cases. Prophylaxis with human rabies immunoglobin (HR16), which gives immediate passive immunity, and human diploid cell vaccine (HDCV) should be given. The current guidelines for rabies vaccination are as follows:

- **Preventive vaccination** (no exposure) (usually 3 doses)
  - Those at high risk of exposure to rabies (veterinarians, animal handlers, rabies lab workers, etc.) should be offered the vaccine.
  - Those in frequent contact with rabies virus or potentially rabid animals (e.g., an international traveler who is likely to come into contact with animals in a region where rabies is common) should be offered the vaccine.
- **Vaccination post-exposure**
  - Those who have been bitten by an animal or may have been exposed to rabies should receive wound cleaning and started on vaccine.
    - **If never vaccinated against rabies previously**: 4 doses (1 dose right away and additional doses on days 3, 7, and 14); give rabies immune globulin at first dose
    - **If vaccinated against rabies previously**: 2 doses (1 dose right away and another on day 3); no need to give rabies immune globulin

Snakebites

Although 50,000 snakebites are reported per year worldwide, only about 8,000 are poisonous. There are <5–10 deaths per year, with rattlesnakes accounting for almost all fatalities.

Snake venom contains numerous potentially dangerous substances such as hemolysis toxin, cardiotoxin, neurotoxin, and proteolytic enzymes. Some of these substances can result in neuromuscular blockade.

Factors which affect the severity of the bite:

- **Body size**: The smaller the body, the worse the effect; thus, bites tend to be worse in children.
- **Location of bite**: Trunk and face bites are worse than extremity bites.
- **Exercising after bite**: Muscular activity helps spread the venom through the lymphatics (so minimize physical activity).
- **Depth of injury**: No poisoning occurs in 20–50% of bites because they are too superficial.

Treatment. Transport the patient immediately to the nearest medical facility.

- **Immobilize**: will help decrease the spread of venom through the lymphatics, which increases with muscular contraction
- **Apply compression bandage**: will help to decrease lymph flow; be sure not to apply so tightly that it decreases venous flow
- **Antivenin**: be cautious of anaphylactic reaction that may occur to the horse serum
- **Supportive**: manage hypotension with fluids; ventilatory support may be necessary

Ineffective therapy includes incision and suction of the bites. Tourniquets and ice immersion do not help and might be harmful.

Note

All venomous snakes are capable of biting a person without injecting venom. They may deliver a "dry bite" rather than waste their venom on a creature too large for them to eat.

Note

Identification of the snake is very important in planning treatment, but it is not always possible. However, in North America, polyvalent antivenoms are available, so snake identification is not high priority.

Neurology 11

Learning Objectives

- Outline the presentation, diagnosis, and management of diseases of the spinal cord including spinal cord compression, syringomyelia, subacute combined degeneration, anterior spinal artery occlusion, ALS, and Brown-Sequard syndrome
- Describe the epidemiology, classification, and treatment of seizures and epilepsy
- Describe the presentation, diagnosis, and management of movement disorders including benign essential tremor, restless leg syndrome, Huntington disease, and Parkinson disease
- Present the diagnosis and management of autoimmune neurological diseases, including Guillain-Barre syndrome, MS, and myasthenia gravis
- Provide a differential diagnosis and work-up of patients presenting with headache, vertigo, or dizziness
- List the criteria for prevention of cerebrovascular accident in patients with TIA, and outline the management of patients with acute cerebrovascular accident
- Describe the epidemiology of dementia and typical course and complications

DISEASES OF THE SPINAL CORD

Spinal Cord Compression

A 63-year-old African-American man is brought to the ED with back pain that started gradually 3 days ago. The patient describes the pain as "band-like" around the abdomen, but not radiating. His past medical history is significant for prostate cancer 3 years ago, which was treated with radiation.

Spinal cord compression (**neurologic emergency**) is an acute syndrome of back pain, associated with compression of the spinal cord. Common causes include cancer, herniated disk, epidural abscess, hematoma, and trauma.

Note

Spinal Cord Compression

Acute: trauma

Subacute: neoplasm most common cause

Chronic: herniation

Symptoms include:

- Pain (**earliest symptom**) which may intensify with actions that increase intrathoracic (and thus CSF) pressure
- Insidious onset of mild sensory disturbance
- Lower extremity weakness
- Sphincter or sexual dysfunction

Acute spinal cord compression has to be suspected on the basis of the history and neurologic exam; that is essential for instituting appropriate treatment early on. Cancer, fever, or bowel/bladder incontinence/retention in the clinical history would strongly suggest this diagnosis. Also, neurologic exam will show:

- Dermatomal sensory level with bilateral lower extremity weakness
- Increased lower extremity muscle tone
- Upper motor neuron signs below the level of compression

The thoracic cord (**most common site of compression, 70%**) is frequently involved because the spinal cord is narrowest at that point. Symptoms may progress quickly.

Diagnosis.

- MRI of the spine (**test of choice**)
- Abnormal plain x-ray (very common but rarely done)
- CT myelogram if MRI is contraindicated

Treatment. Once the diagnosis is suspected, start high-dose dexamethasone immediately. After the specific etiology is identified more clearly by MRI, initiate specific therapy:

- **For a radiosensitive tumor, e.g., lymphoma or multiple myeloma**: radiation therapy as soon as possible
- **For herniated disk, epidural abscess, or hematoma**: surgical decompression

Prognosis depends mainly on the functional status of the patient at the time of presentation. Up to 80% of patients who are initially able to ambulate retain that ability after treatment. Only 5% of patients without antigravity leg strength are able to ambulate after treatment.

Syringomyelia

Syringomyelia is cavitation of the spinal cord. It occurs as communicating (with the CSF pathways) or noncommunicating.

- **Communicating** syringomyelia is usually associated with the congenital Arnold Chiari malformation.
- **Noncommunicating** syringomyelia is typically secondary to trauma or tumors of the spinal cord.

In the cervical vertebrae of both gray and white matter, there is typically sensory dissociation with impaired pain and temperature and intact sensation to light touch. The loss of pain and temperature occurs in a cape-like distribution across the neck and arms. There is sparing of tactile sensation, position, and vibratory sense. Reflexes are lost.

As the lesion enlarges, there may be lower motor neuron manifestations at the level of the lesion with upper motor neuron signs below the lesion. Cavitation most commonly occurs at the level of the cervical cord. MRI is the most accurate diagnostic test. Treatment is surgical, but often unsatisfactory.

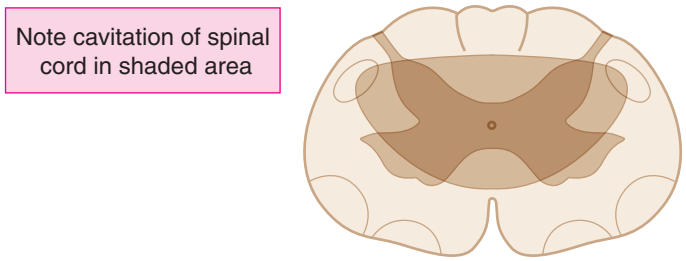


Figure 11-1. Syringomyelia

Subacute Combined Degeneration

Subacute combined degeneration occurs with vitamin B12 deficiency. Patients will complain of distal paresthesias and weakness of the extremities followed by spastic paresis and ataxia. On exam there is a combined deficit of vibration and proprioception with pyramidal signs (plantar extension and hyperreflexia).

Diagnosis is made with low vitamin B12 level. Treatment is vitamin B12 replacement.

Anterior Spinal Artery Occlusion

Anterior spinal artery occlusion presents with acute onset of flaccid paralysis that evolves into a spastic paresis over days to weeks. Additionally, there is loss of pain and temperature sensation with sparing of vibration and position sense as the posterior columns are supplied by the posterior spinal artery. Everything (motor, sensory, autonomic) is lost below the level of the infarction with the striking exception of retained vibration and position sense.

Treatment is supportive.

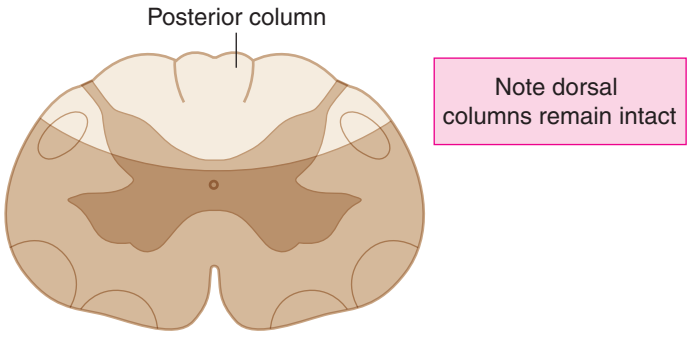


Figure 11-2. Anterior Spinal Artery Occlusion

Brown-Séquard Syndrome

Hemisection of the cord results in a lesion of each of the 3 main neural systems:

- Principal upper motoneuron pathway of the corticospinal tract
- One or both dorsal columns
- Spinothalamic tract

Presentation of 2 ipsilateral signs and 1 contralateral sign is the **hallmark sign** of a lesion.

- A lesion of the corticospinal tract results in an ipsilateral spastic paresis below the level of the injury.
- A lesion to the fasciculus gracilis or cuneatus results in an ipsilateral loss of joint position sense, tactile discrimination, and vibratory sensations below the lesion.
- A lesion of the spinothalamic tract results in a contralateral loss of pain and temperature sensation starting 1 or 2 segments below the level of the lesion.

At the level of the lesion, there will be an ipsilateral loss of all sensation, including touch modalities as well as pain and temperature, and an ipsilateral flaccid paralysis in muscles supplied by the injured spinal cord segments.

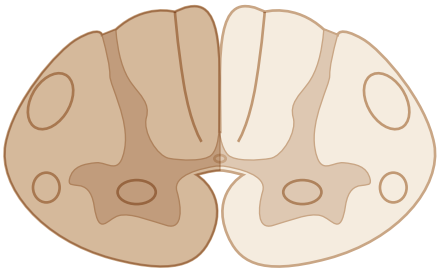


Figure 11-3. Hemisection: Brown-Séquard Syndrome

Clinical Recall

Which of the following is not a symptom of spinal cord compression?

A. Sensory disturbance

B. Back pain

C. Visual disturbance

D. Sexual dysfunction

E. Sphincter dysfunction

Answer: C

Epidural Abscess

Epidural abscess is a rare but serious infection, usually in the spinal epidural space.

Symptoms include:

- Fever
- Leukocytosis
- Back pain
- Spinal cord dysfunction (weakness or even paralysis)
- Bladder/bowel dysfunction
- Hyperreflexia
- Possible discitis (infection of the spinal discs)

Diagnosis. Prompt evaluation with MRI is critical. Blood cultures and sampling of the abscess for the pathogen are crucial.

The bacteria most likely to be seen is *Staphylococcus aureus*, but other pathogens are also seen. MRSA is not uncommon and should be considered.

TB, as well as geographic fungi (and even brucellosis), may be causal.

Treatment should be directed at the pathogen diagnosed, with early antimicrobial therapy. On occasion surgical drainage and laminectomy are required.

Note

As *Staphylococcus aureus* is such a common cause of epidural abscess, risk factors include:

- IV drug use
- Tattoos, acupuncture
- Staph bloodstream infections, e.g., endocarditis

CEREBRAL DISORDERS

Cerebrovascular Accident (Stroke)

> A 56-year-old woman is brought to the ED by her daughter with sudden onset of right upper extremity weakness that began while watching television earlier. The daughter became concerned when her mother was unable to talk in response to questions. Neurologic exam shows right upper extremity weakness with pronator drift and right facial nerve palsy. When questioned, the patient seems to understand what is being said but cannot clearly respond.

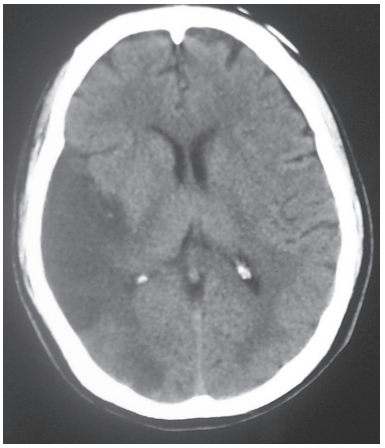
Cerebrovascular accident (CVA), or stroke, is the sudden onset of a focal neurologic deficit. The principal mechanisms by which stroke occurs are:

- Large artery thrombosis
- Small artery thrombosis (lacunar)
- Embolic (cardiogenic or artery-to-artery)
- Vascular dissection
- Systemic hypertension
- Bleeding

Clinical Presentation. Stroke should be considered in any patient who presents with acute onset of a focal neurologic deficit. The specific clinical syndrome is determined by the mechanism and vascular territory affected.

The blood supply to the brain is divided into 2 systems: the carotid (anterior) circulation and the vertebrobasilar (posterior) circulation. The major blood vessels comprising the anterior circulation include the anterior cerebral artery (ACA) and middle cerebral artery (MCA).

- **Occlusion of the ACA** presents with contralateral weakness and sensory loss in the leg more than in the upper extremity. Urinary incontinence, confusion, and behavioral disturbances are common. Lower extremity weakness exceeds upper extremity weakness.
- **Occlusion of the MCA** presents with contralateral hemiplegia, hemisensory loss, and homonymous hemianopia with eyes deviated toward the cortical lesion. Dominant hemisphere involvement results in aphasia. Nondominant hemisphere involvement results in preserved speech, comprehension with confusion, and apraxia with spatial and constructional deficits.



aic.cuhk.edu.hk/web8

Figure 11-4. CT Scan of a Right MCA Infarction

The posterior circulation provides blood supply to the cerebellum, brainstem, occipital lobe of the cortex, and pons. The major blood vessels that comprise the posterior circulation are the posterior cerebral artery (PCA), basilar artery (BA), and vertebral arteries.

Table 11-1. Posterior Circulation Syndromes

	Ipsilateral	Contralateral
Weber	CN III	Hemiplegia
Benedikt	CN III	Ataxia
Wallenberg	Facial sensory loss	Body sensory loss

Specific syndromes associated with occlusion of basilar artery branches include the "locked-in syndrome" (paramedian branches), presenting as quadriparesis with intact vertical eye movements; and Wallenberg syndrome (posterior inferior cerebellar artery), which presents as ipsilateral facial sensory loss, contralateral body sensory loss, vertigo, ataxia, dysarthria, dysphagia, and Horner syndrome.

Occlusion of the major cerebellar arteries produces vertigo, vomiting, nystagmus, and ipsilateral limb ataxia.

Diagnosis.

- Noncontrast CT of the head (**initial test of choice**) to distinguish between hemorrhagic and ischemic stroke; it is often negative for ischemia within first 48 hours
- Diffusion-weighted MRI (**most accurate test for detecting cerebral ischemia**)

For acute ischemic stroke, the work-up involves searching for embolic sources (echocardiogram, carotid duplex, and 24-hour Holter monitor). Also consider a work-up for inherited hypercoagulability.

Subarachnoid hemorrhage is associated with ECG abnormalities such as ischemia or inverted T-waves ("cerebral T-waves"). A "bubble study" is done on the echocardiogram to detect the presence of a patent foramen ovale or other cardiac defect.

Treatment.

- Tissue plasminogen activator (tPA) if patient presents within 3 hours of symptoms; contraindications for tPA include:
  - Stroke or serious head trauma within 3 months
  - Hemorrhage (GI or GU) within 21 days
  - Surgery within 14 days
  - History of intracranial hemorrhage
  - BP >185/110 mm Hg
  - Current use of anticoagulants
  - Platelets <100,000/mm^3
  - Coagulopathy (PT >15 seconds)
- Antiplatelet therapy for secondary prevention of ischemic stroke
- Aspirin (**first-line**); start 24 hours after tPA
  - When there is known allergy to aspirin or recurrent cerebrovascular events on aspirin alone, add dipyridamole or switch to clopidogrel to enhance antiplatelet therapy.
  - **Do not combine** aspirin and clopidogrel for a stroke.
- Ticlopidine is no longer used because the rates of thrombotic thrombocytopenic purpura and leukopenia are unacceptably high.
- Nimodipine for subarachnoid hemorrhage, to reduce the risk of ischemic stroke
- Early surgical intervention (within several days) to clip off aneurysm or embolize the vessel with a catheter, for good operative candidates
  - Do not wait for unrepaired aneurysm to rebleed
  - Repair unruptured aneurysms found incidentally if >10 mm in size

Note

Noncontrast CT is the most sensitive test for detecting blood in the brain.

Note

Patients who receive tPA in an appropriate manner have better neurologic function 3 months after CVA, as compared with those who do not receive it.

- For **symptomatic** carotid stenosis when occlusion >70% of the arterial lumen, endarterectomy is recommended (the more severe the disease, the greater the benefit). Carotid stenting is an alternative. For **asymptomatic** carotid stenosis, the effectiveness of endarterectomy is not clear; it may benefit when >60% stenosis in men age <60, but is less clear in women because they have a lower risk of stroke.

Note

Combination of antiplatelet agents is used in coronary disease but **not in cerebral disease**.

Endarterectomy is better than carotid angioplasty and stenting for symptomatic patients with >70% stenosis. Angioplasty and stenting should be considered only for those who cannot undergo surgical endarterectomy.

Transient ischemic attack

TIA (transient ischemic attack), or "mini-stroke," is a sudden finding of neurological dysfunction (blood supply to the brain is temporarily blocked) that resolves within 24 hours. It is likely of the same pathogenesis as a true stroke, and the risk of recurrent events—including completed strokes—is very high.

Note

Heparin has no clear benefit with stroke. That is because of the increased risk of bleeding. Any benefit is offset by adverse events associated with treatment. For every stroke prevented, one intracranial hemorrhage is caused.

Therefore, full evaluation is recommended:

- Cardiac evaluation
- Visualization of the carotids

Treatment of TIA is prompt initiation of antiplatelet agents. If patients begin improving within a few hours, there is no benefit to thrombolytic therapy.

Seizures and Epilepsy

> A 29-year-old man is brought to the ED after being found convulsing in his bedroom. His mother says that during the episode, her son was unable to respond to her frantic cries. She describes jerking movements that became more frequent and then stopped after a minute. Then, for at least 20 minutes after the episode, he seemed tired and lethargic.

A seizure is a paroxysmal event due to abnormally discharging CNS neurons. Epilepsy is a condition involving recurrent seizures, due to a chronic underlying process.

Causes of seizure can be remembered with the acronym “VITAMINS”:

- **V**ascular (stroke, bleed, arteriovenous malformation)
- **I**nfection (meningitis, abscess, encephalitis)
- **T**rauma (especially penetrating)
- **A**utoimmune (CNS vasculitis)
- **M**etabolic (hyponatremia, hypocalcemia, hypomagnesemia, hypoglycemia, hypoxia, drug overdose/withdrawal)
- **I**diopathic
- **N**eoplasm
- P**S**ychiatric

A seizure is essentially a paroxysmal, involuntary event (associated with abnormal movement or change of consciousness or both).

- Sudden in onset, with or without an aura
- Disorientation, sleepiness, and aching muscles for minutes to hours after the event
- Incontinence, tongue-biting, and headache as a result of the seizure

Classification of seizures according to their clinical features is important in that it will determine the medications used for treatment.

The first classification is **partial** versus **generalized**. The next classification is **simple** versus **complex**.

- **Partial** seizure occurs within discrete portions of the brain. Symptoms include involuntary jerking of a finger or hand.
  - If consciousness is maintained for the duration of the seizure, that is a **simple** partial seizure. If there is a *change in consciousness* for the duration of the seizure, that is a **complex** partial seizure.
  - When a partial seizure progresses to a generalized seizure, that is a **partial seizure with secondary generalization**. Typically, the seizure will begin focally and become generalized as seizure activity involves both cerebral hemispheres.
- **Generalized seizure** arises from both cerebral hemispheres spontaneously without any detectable focal onset.
  - **Generalized tonic-clonic (grand mal)** seizure is characterized by tonic contraction of muscles throughout the body followed by intermittent relaxation of various muscle groups (clonic phase).
  - **Absence (petit mal)** seizure (children > adults) is characterized by sudden, brief loss of consciousness without loss of postural tone. EEG will show a generalized, symmetric 3-Hz spike-and-wave discharge pattern. **Atonic** seizure is characterized by sudden loss of postural tone lasting 1–2 seconds. **Myoclonic** seizure is characterized by sudden, brief muscle contraction.

Status epilepticus is defined as recurrent or continuous seizures (lasting at least 5–30 min).

Diagnosis. For idiopathic seizure, diagnosis is made only after secondary precipitating factors have been ruled out. For epilepsy, diagnosis is done with EEG. However, an abnormal EEG alone is not diagnostic, as 2–18% of the population has an abnormal EEG. Always check serum electrolytes, glucose, toxicology, and arterial blood gas to rule out hypoxia as a cause of a patient's seizure. CT scan or MRI of the head is usually indicated to rule out a structural lesion as the cause of seizure. Think of any seizure as a symptom, much like shortness of breath or chest pain, that has an extensive differential diagnosis. The evaluation of any seizing patient is to rule out reversible causes of seizure.

Treatment of seizure can be divided into management for the acutely seizing patient (status epilepticus) and the chronic epileptic patient.

Clinical Correlate

It may be difficult to differentiate **seizure** from **syncope**. Be sure to obtain a history from anyone who witnessed the event.

- Syncope does not often present with significant postictal symptoms.
- Patients recover consciousness within several minutes.
- There is no incontinence or tongue-biting afterward.

In the **acutely seizing patient**:

- Secure the **a**irway, **b**reathing, and **c**irculation.
- Once an airway is established, breathing is assured, and patient is hemodynamically stable, then simultaneously evaluate and treat any precipitating cause of seizure. If a reversible cause is identified, treat aggressively.
- If patient continues to seize, then give a benzodiazepine (lorazepam or diazepam) (**drugs of choice**), which will potentiate GABA receptor function. Side effects of phenytoin include CNS (diplopia, dizziness, and ataxia) and systemic (gum hyperplasia, lymphadenopathy, hirsutism, and rash).
- If patient continues to seize, add phenytoin or fosphenytoin, which will inhibit sodium-dependent action potentials.
- If patient continues to seize, add phenobarbital. Side effects include sedation, ataxia, and rash.
- If, despite all of the treatments, patient continues to seize, add midazolam or propofol.

In patients with **first-time seizure**, start anticonvulsant therapy **only** if patient has:

- Abnormal neurologic exam
- Presented with status epilepticus
- Strong family history of seizure
- Abnormal EEG

Otherwise, first-time seizure is generally not treated with long-term anticonvulsant therapy.

Note

There is no superior drug for seizures during pregnancy. Valproic acid is clearly more dangerous in pregnancy.

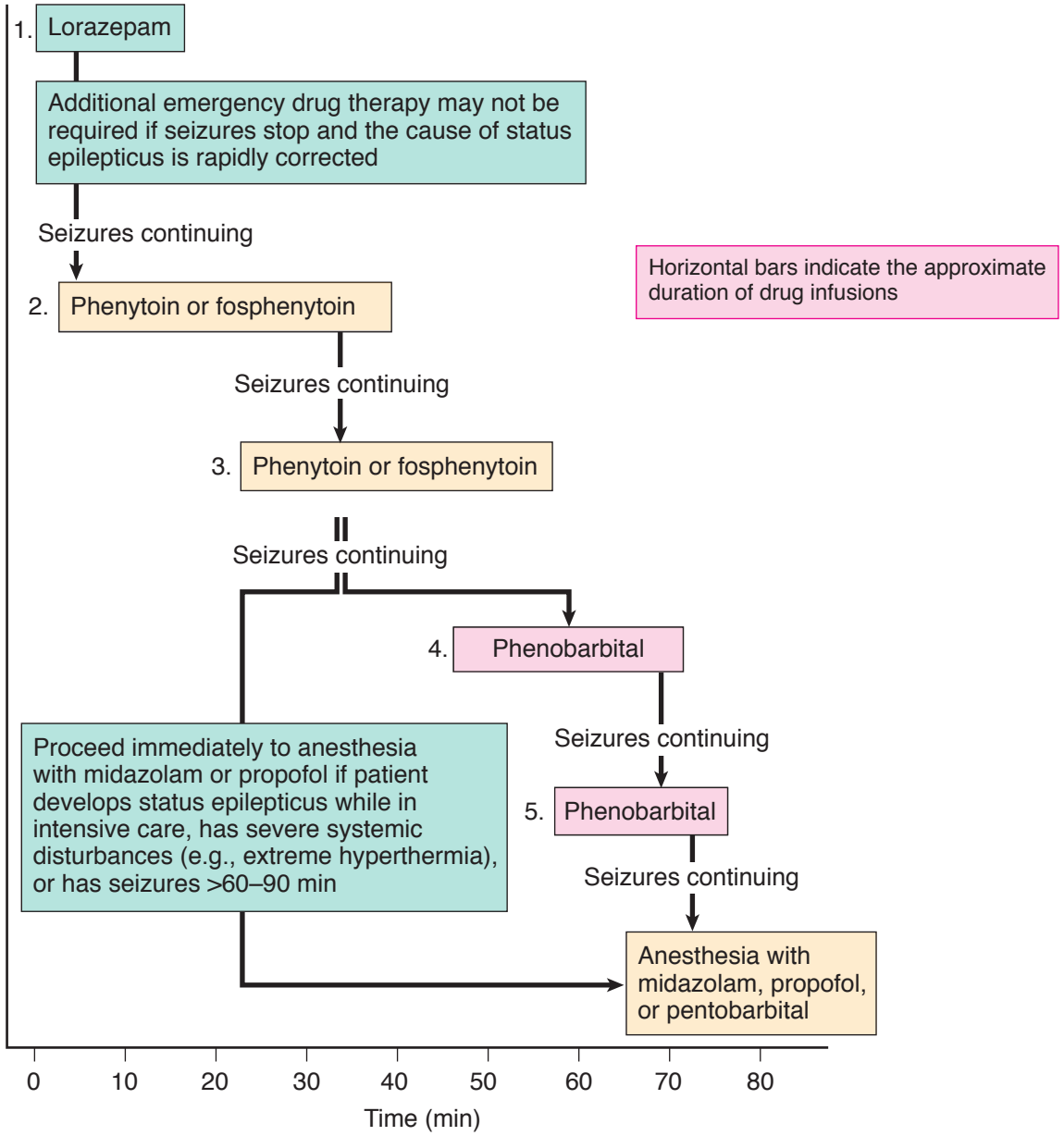


Figure 11-5. Development of Status Epilepticus

Treatment. There is no single antiepileptic drug that is superior to the others. Valproic acid, phenytoin, levetiracetam, and carbamazepine are nearly equal in efficacy.

- **Primary generalized tonic-clonic seizure** is treated with valproic acid, phenytoin, lamotrigine, carbamazepine, or levetiracetam. Lamotrigine works by decreasing glutamate release. Side effects include Stevens-Johnson syndrome.
- **Absence seizure** is treated with ethosuximide (**first-line**). Valproic acid is an alternative.

- **Myoclonic and atonic seizure** is treated with valproic acid (**first-line**).
- **Partial seizure**—whether complex or simple, and whether progressed to secondary generalized seizure—is treated with carbamazepine and phenytoin (**first-line**). Valproic acid, lamotrigine, and levetiracetam are alternatives.

Knowing when to stop treatment is difficult for the clinician.

- One option is to stop if the patient has been free of seizures for 2–3 years.
- Another option is to do a sleep-deprivation EEG to evaluate the patient's risk of recurrence. A normal test means a lower likelihood of seizures.

Clinical Recall

Which of the following symptoms are seen in Wallenberg syndrome?

A. CN III palsy with contralateral ataxia

B. Quadriparesis with intact vertical eye movements

C. Vertigo, nystagmus, and ipsilateral limb ataxia

D. Weakness and sensory loss of lower extremities

E. Facial nerve palsy, dysarthria, dysphagia, and Horner syndrome

Answer: E

Dementia

A 67-year-old woman is brought to the clinic with complaints of forgetfulness. She explains that she has been forgetting common phone numbers and the name of her mailman, whom she has known for 25 years. Her past medical history is significant for hypertension, coronary artery disease, and high cholesterol. Her physical examination is unremarkable.

Cognitive function is measured by various mental functions, including memory, concentration, language, praxis, visuospatial functioning, and executive functions. "Dementia" refers to loss of memory with impairment of any other cognitive function sufficient to interfere with social or occupational functioning.

There are more than 100 identifiable causes of dementia in the elderly.

- **Reversible causes** include hypothyroidism, vitamin B12 deficiency, hepatic or uremic encephalopathy, CNS vasculitis, syphilis, brain abscess, brain tumor (primary or metastatic), medications (especially anticholinergics), obstructive sleep apnea, central sleep apnea, trauma, subdural hematoma, normal pressure hydrocephalus (NPH), and depression.
- **Irreversible causes** include progressive multifocal leukoencephalopathy, **Alzheimer disease (60-80% of all cases)**, dementia with Lewy bodies, frontotemporal degeneration including Pick disease, vascular dementia including multi-infarct dementia and Binswanger disease, and Creutzfeldt-Jakob disease (CJD).

Note

- By age 65–69, the prevalence of dementia is 1–5%.
- By age 100, the prevalence of dementia is 45%.
- Only 5% of Alzheimer disease is inherited.

Clinical Presentation. The most common cause of dementia is Alzheimer disease. Typically, patients will present with problems in memory and visuospatial abilities that generally occur early in the course of the disease. Social graces can be retained despite significant loss of cognitive decline. Hallucinations and personality changes typically occur late in the course of the disease.

Mild cognitive impairment refers to memory loss without dysfunction of other cognitive domains. These patients have a higher risk of developing Alzheimer disease later in life but do not have Alzheimer disease. The rate of progression is 15–20% per year.

Alzheimer disease is, by definition, the loss of memory as well as other cognitive disturbances such as aphasia, agnosia (the failure to identify entities despite intact sensory function), apraxia, or the loss of the ability to make plans and execute them. There is no single diagnostic test for Alzheimer disease.

Patients with frontotemporal dementias such as Pick disease will typically present with personality changes early in the course of their disease, with relative sparing of their visuospatial function. Social, interpersonal, and emotional abnormalities precede memory impairment. Frontotemporal dementia is often noted primarily by the family because the patient lacks insight into their condition. There is no proven therapy for this condition.

Dementia with Lewy bodies (DLB) can be confused with delirium and is characterized by fluctuating cognitive impairment.

Dementia secondary to Parkinson disease should be accompanied by clinical findings consistent with that disease. Recurrent visual hallucinations are also characteristic.

Dementia secondary to CJD is characterized by a shorter (weeks to months), more aggressive course than Alzheimer disease. Patients with CJD will present with dementia and myoclonus. Variant CJD is bovine spongiform encephalopathy (BSE). BSE is from the ingestion of prions from affected cattle. The diagnosis of CJD is by rapidly progressive dementia, myoclonus, ataxia, and the presence of 14-3-3 protein in the CSF. EEG may also help diagnose. These criteria can eliminate the need for brain biopsy.

Vascular dementia is divided into multi-infarct dementia, which typically has a stepwise progression associated with discrete cerebrovascular events, and Binswanger disease, involving the subcortical white matter, which presents with a slowly progressive course.

Normal pressure hydrocephalus will present with prominent gait abnormalities early in the course of the disease that usually precede the onset of cognitive impairment. There will also be associated urinary incontinence.

Diagnosis. All patients with cognitive impairment should be assessed with a Mini Mental Status Examination (MMSE) to identify the areas of cognitive impairment.

Initially, the work-up should focus on ruling out reversible causes of the dementia. If a reversible cause is identified it should be treated, with the hope that cognitive function can be recovered. Laboratory studies should include a complete blood count (CBC), electrolytes, calcium, creatinine, liver function studies, glucose, thyroid-stimulating hormone (TSH), vitamin B12, RPR, and HIV.

Brain imaging is most useful for patients who have a focal neurologic exam, seizures, gait abnormalities, and an acute or subacute onset of their symptoms. EEG and CSF evaluation are not necessary except for NPH-opening pressure. No CSF marker is proven beneficial, with the exception of 14-3-3 protein in CJD.

Treatment. Treatment of dementia revolves around ensuring that the family and the patient have the proper medical and emotional support to cope with the disease. Caregivers are at an increased risk for depression and anxiety. Their concerns and frustrations should be addressed at frequent intervals.

Raising the level of acetylcholine in CSF benefits patients with Alzheimer disease. Pharmacotherapy with donepezil has been shown to improve cognitive function in mild to moderate dementia. Other anticholinesterase inhibitors (rivastigmine, galantamine) appear to have similar efficacy.

Memantine is a disease-modifying drug used in advanced disease, either alone or with a cholinesterase inhibitor. Memantine seems to be neuroprotective and reduces the rate of progression of disease.

Subdural Hematoma

Subdural hematomas (also see Emergency Medicine) are venous bleeds that form between the dura and arachnoid membranes. They are caused by bleeding from small veins in this areas after trauma.

Diagnosis is (easily) made with CT scan without contrast.

Treatment.

Note

With subdural hematoma, corticosteroids are not helpful.

- **Small hematomas with minimal neurologic impairment**: nonsurgical management
  - Consider reversing anticoagulation
  - Monitor neurologic status and repeat CT imaging to see if hematoma is expanding
- **Large hematomas or evidence of severe neurologic dysfunction**: prompt surgical drainage

PAIN AND SENSORY DISORDERS

Vertigo and Dizziness

> A 53-year-old woman presents at the ED with complaints of dizziness. She describes walking to the bathroom and experiencing a sudden feeling of nausea. She then vomited and fell to the floor. She was unable to get up but was able to call 911. The patient describes a feeling of the room "spinning" around her, even though she realizes she was not moving.

Vertigo is a false sensation of movement, i.e., the sensation of movement in the absence of actual movement. It may be caused by Ménière disease, labyrinthitis, positional vertigo, traumatic vertigo, perilymphatic fistula, and cervical vertigo. Other causes include vascular disease of the brainstem, arteriovenous malformation, brain tumor, MS, drug overdose, and vertebrobasilar migraine.

With the dizzy patient, the first step is to determine the nature of the patient's complaints. "Dizziness" is a nonspecific term that provides no meaningful information about what is occurring to the patient. Simply by taking a complete history, it is possible to determine whether the patient is experiencing vertigo or presyncope.

Patients who experience vertigo will describe a sensation of movement without actually moving. They often describe their environment "spinning around them." Sensations of tilting, swaying, or falling forward or backward are all consistent with vertigo. Acutely, these episodes are commonly associated with nausea and vomiting.

Patients who complain of presyncope will describe their symptoms as "lightheadedness" or "feeling like I'm going to black out." Associated symptoms include generalized weakness, palpitations, and shortness of breath. It is essential to differentiate vertigo from presyncope because vertigo is usually a manifestation of neurologic disease, whereas presyncope is a cardinal manifestation of cardiovascular disease.

Once you are convinced by the history that the patient is indeed experiencing vertigo, determine whether the vertigo is **secondary to peripheral** or **central vestibular disease** (management will differ). Several points on history and physical examination will help to distinguish them.

Table 11-2. Vertigo

	Central Vertigo	Peripheral Vertigo
Onset	Gradual	Usually sudden
Tinnitus, hearing loss	Absent	Present
Neighborhood signs (diplopia, cortical blindness, dysarthria, extremity weakness/numbness)	Present	Absent
Nystagmus	Pure, vertical, does not suppress with fixation, and multidirectional	Mixed, horizontal, suppresses with fixation, and unidirectional

Once you have determined that the patient has peripheral vertigo, there is a wide differential diagnosis that should be considered.

- **Ménière disease** is characterized by tinnitus, hearing loss, and episodic vertigo. Each episode lasts 1 to 8 hours. Symptoms wax and wane as the endolymphatic pressure rises and falls. The most common are syphilis and head trauma.
- **Benign paroxysmal positional vertigo** is a cause of peripheral vertigo that characteristically is exacerbated by head movement or change in head position. It may be associated with nystagmus, perhaps caused by calculi on the semicircular canals. There is a latency of several seconds after head movement before the onset of vertigo, and the vertigo usually lasts up to 60 seconds. Episodes occur in clusters which persist for several days.
- **Labyrinthitis** presents with sudden onset of severe vertigo that lasts for several days with hearing loss and tinnitus. The disease frequently follows an upper respiratory tract infection.
- **Perilymphatic fistula** is a form of peripheral vertigo related temporally to head trauma (blunt trauma to the ear, e.g., a slap to the ear) or extreme barotrauma during air flight, scuba diving, or vigorous Valsalva maneuver. Explosions deafen people.
- **Central vertigo** is caused by any cerebellar or brainstem tumor, bleed, or ischemia. Drug toxicity/overdose is a common cause. In the young patient with unexplained central vertigo, consider MS.

Treatment. Symptomatic treatment for peripheral vertigo includes meclizine or, in severe cases, diazepam.

- **Ménière disease**: low-salt diet and diuretics; if no response, consider surgical decompression
- **Benign paroxysmal positional vertigo**:
  - Dix Hallpike and Barany maneuvers, positional maneuvers that attempt to move the otolith out of the circular canals
  - Epley maneuver, which attempts to reposition the head by dislodging the calculi; the examiner holds the (seated) patient's head and rotates it to the side as he moves the patient into a lying position
- Vertigo secondary to **labyrinthitis**: meclizine and diazepam when symptoms are severe; steroids are helpful

Note

Patients may be taught to do a modified Epley maneuver at home.

Headache

> A 32-year-old woman presents with headache for 2 days. She says it is at the right side of her head and it is throbbing. Things that seem to worsen the pain include walking up stairs or around the block, bright light, and loud noise. She experiences nausea but denies vomiting.

Headache is defined as pain located in the head, neck, or jaw. There are many causes.

- **Primary headache syndromes** include migraine (15% of the general population), cluster, and tension headache.
- **Secondary causes of headache** include intracranial hemorrhage, brain tumor, meningitis, temporal arteritis, and glaucoma.

The most important question to answer with a complaint of headache is whether a serious underlying cause exists for the symptoms. Do this with a thorough history and physical examination.

- Is this the patient's first episode of headache? A history of recurrent symptoms suggests a primary headache disorder, while a first-time headache—especially severe and rapidly peaking—suggests a serious underlying pathology.
  - Headache with fever and nuchal rigidity suggests meningitis.
  - Headache described as "the worst headache of my life" and/or "thunderclap" at onset, accompanied by nuchal rigidity without fever, suggests an intracranial hemorrhage.
  - Headache described as a deep, dull, aching pain and that disturbs sleep suggests a brain tumor.
  - A history of vomiting that precedes the onset of headache by a number of weeks, or a history of headache induced by coughing, lifting, or bending, suggests a posterior fossa brain tumor.

Note

Any patient who presents with headache and the following should be considered to have a secondary headache syndrome:

- "Worst headache of my life"
- Worsening symptoms over days to weeks
- Abnormal neurologic exam
- Fever
- Vomiting preceding the headache
- Headache induced by coughing, bending, lifting, or onset age >55

  - Unilateral pounding headache associated with visual changes described as dull and boring with superimposed lancinating pain suggests temporal arteritis.
    - Commonly seen age >50
    - Symptoms also include polymyalgia rheumatica, jaw claudication, fever, weight loss, and scalp tenderness (difficulty combing hair/lying on a pillow) (scalp tenderness is due to pain over the temporal artery).
    - Causes sedimentation rate to elevate
    - Diagnosed with biopsy of the temporal artery
    - Do not wait for the biopsy results to initiate therapy with steroids.
  - History of eye pain preceding the onset of headache suggests glaucoma.
- Once serious underlying pathology is excluded by history and physical examination, consider a primary headache syndrome: migraine, tension, or cluster headache.

Migraine headache

Migraine headache is a benign and recurrent syndrome of headache, nausea/vomiting, and other varying neurologic dysfunction.

- Pulsatile, throbbing, unilateral, and aggravated by minor movement
- Present with photophobia and phonophobia
- Time to maximal pain is 4–72 hours

Migraine is a likely diagnosis when a typical trigger can be identified. Alcohol, chocolate, certain cheeses, monosodium glutamate, hunger, and irregular sleep patterns are common triggers.

- **Migraine without aura** (**more common**) is a migraine without a preceding focal neurologic deficit.
- **Migraine with aura** (**classic migraine**) is accompanied by a preceding aura that consists of motor, sensory, or visual symptoms. Focal neurologic symptoms usually occur during the headache rather than as a prodrome. The pathognomonic aura for classic migraine is the scintillating scotoma. Visual auras are also described as stars, sparks, and flashes of light. Migraine equivalent is defined as focal neurologic symptoms without the classic complaints of headache, nausea, and vomiting.
- Complicated migraine is migraine with severe neurologic deficits that persist after the resolution of pain.
- Basilar migraine is migraine associated with symptoms consistent with brainstem involvement (vertigo, diplopia, ataxia, or dysarthria).

Tension headache

Tension headache is a tight, band-like headache that occurs bilaterally. The pain is "vise-like," and possibly associated with tightness of the posterior neck muscles. The pain builds slowly and may last for several days with or without fluctuations. Movement does not generally exacerbate the headache.

Cluster headache

Cluster headache (men > women) begins without warning.

- Excruciating, unilateral, periorbital
- Peaks in intensity within 5 minutes of onset
- Rarely pulsatile in nature
- Lasts from 30 minutes to 3 hours, and occurs 1–3× day for 4–8 weeks
- Symptoms include rhinorrhea, reddening of the eye, lacrimation, nasal stuffiness, nausea, and sensitivity to alcohol.
- Horner syndrome may be seen.
- Emotion and food will rarely trigger a cluster headache.

Patients with severe, sudden onset of a first-time headache accompanied by strong evidence for an underlying cause should have a head CT scan to rule out any secondary causes.

Treatment.

- **Migraine headache**
  - **Acute episode** (abortive therapy)
    - Triptans, serotonin receptor agonists (**sumatriptan is first-line**)
    - Dihydroergotamine
    - Ergotamine, used in combination with caffeine, for acute abortive therapy
    - Dopamine antagonists such as metoclopramide: given orally they help absorption of other medications, and when given parenterally they provide fast-acting relief for migraine
  - **Prophylaxis** (for acute migraine headache >3–4/month)
    - Beta blocker: propranolol, valproic acid, and topiramate (**all first-line**)
    - Verapamil and tricyclics (require 2–6 weeks for full effect)
    - SSRIs such as sertraline and fluoxetine
- **Tension headache**
  - Relaxation methods
  - NSAIDs and acetaminophen
  - If no response, add a muscle relaxant
- **Cluster headache**
  - Triptan or 100% oxygen
  - CCB (prophylaxis); prednisone and lithium are alternatives

Note

Triptans are contraindicated in known cardiovascular disease, uncontrolled hypertension, and pregnancy.

For migraine treatment, caution with the following medications:

- Methysergide, because of the serious side effects associated with prolonged use (valvular and retroperitoneal fibrosis)
- Opioid analgesics, because of their potential for addiction; use only for severe, infrequent migraines that are unresponsive to other therapy

Table 11-3. Migraine Therapies

Abortive	Prophylactic
• NSAIDs, aspirin, acetaminophen • Triptans • Ergotamine derivatives	• Beta blockers • Calcium blockers • Tricyclics • SSRIs • Valproic acid • Topiramate

Pseudotumor Cerebri

Pseudotumor cerebri (or benign intracranial hypertension) is an idiopathic increase in intracranial pressure. Women > men by 10×.

Often there is no identified cause and the disorder resolves spontaneously after several months. There is an association with obesity, chronic lung disease, Addison disease, oral contraceptives, tetracycline use, and vitamin A toxicity.

Symptoms include:

- Headache
- Visual disturbances such as diplopia and papilledema; enlargement of the blind spot on visual field testing
- Sixth cranial nerve (abducens) palsy
- Normal CT, MRI, and CSF beyond an increase in pressure

Treatment.

- Weight loss
- Removal of the offending agent, e.g., oral contraceptives
- Diuretics such as acetazolamide and furosemide
- Steroids such as prednisone
- For urgent cases, repeated lumbar punctures
- If there is no response, possible placement of a surgical shunt between the ventricles and peritoneum

Trigeminal Neuralgia

Trigeminal neuralgia (or tic douloureux) is an idiopathic pain syndrome that causes sudden, sharp pain starting near the side of the mouth and progressing to the ear, eye, or nostril. Attacks can be triggered by touch or small movements such as talking or eating. The pain lasts for a few seconds and disappears, but it can be extremely severe, and even incapacitating.

Trigeminal neuralgia is felt to be secondary to compression of the trigeminal nerve root by a blood vessel. Occasionally it can be a manifestation of MS or a posterior fossa tumor.

- Despite the pain, the sensory examination will be normal.
- With the exception of MS or the posterior fossa tumor, all imaging and neurologic testing will be normal.

Treatment is carbamazepine (standard of care). If there is no response, try phenytoin, baclofen, or gabapentin.

If still no response, surgery or radiofrequency lesioning into the affected nerve may work.

Clinical Recall

Which of the following are the characteristic features of labyrinthitis?

A. Syphilis induced vertigo, hearing loss, and tinnitus

B. Perilymphatic fistula as a result of head trauma

C. Sudden onset of vertigo following upper respiratory tract infection

D. Vertigo that occurs with changes in head position

E. Central vertigo following toxicity with gentamicin

Answer: C

AUTOIMMUNE DISORDERS

Multiple Sclerosis

A 32-year-old woman presents at the ED complaining of numbness and tingling in her right hand. The symptoms began several days ago and have worsened over the last several hours. Three years ago she had an episode of "seeing double" for 2 days but it resolved on its own. Physical examination is significant for hyperreactive reflexes bilaterally in her lower extremities. Increased spasticity is also noted in the lower extremities.

Multiple sclerosis (MS) is an autoimmune inflammatory disease of the CNS white matter with a relapsing or progressive course. The cause is thought to be multifactorial:

- Genetic susceptibility has been proven.
- Environmental triggers (infectious, climatic, dietary) are suspected, as MS occurs primarily in women of Northern European descent and of child-bearing age, respectively.

Clinical Presentation. Commonly, patients complain of weakness, numbness/tingling, or unsteadiness of a limb. Urinary urgency/retention and blurry/double vision are also seen in early disease. Symptoms may persist for several weeks or just a few days.

Pathologically, focal areas of demyelination are characteristic of the disease.

There are several forms of the disease that may change the course of management. Most patients have a disease-free period (from months to years) after their first exacerbation.

- **Relapsing-remitting disease:** progression is characterized by relapses of active disease with incomplete recovery during the periods of remission
- **Secondary progressive disease:** progression becomes more aggressive so that a consistent worsening of function occurs
- **Primary progressive disease:** symptoms are progressive from the onset of disease with the early onset of disability (least common form)

Infections or trauma may acutely worsen the disease. Pregnancy, especially the 2 to 3 months post-birth, may also exacerbate symptoms. (During the pregnancy itself, there are fewer attacks.) Uncomplicated MS typically has no adverse effects on the outcome of the pregnancy.

Diagnosis. To diagnose MS you have to rely on clinical criteria supplemented with radiologic and laboratory confirmation. Clinically, a young patient (age <55) presents with a history of multiple neurologic complaints that cannot be explained by the presence of one CNS lesion, i.e., when there are multiple neurologic deficits **separated by time and space (anatomy)**.

- MRI of the brain (**most accurate test**) has nearly 95% sensitivity in symptomatic persons.
- Increased T2 and decreased T1 intensity represent the increased water content of demyelinated plaques in the cerebrum and spine.
- Enhancement of lesions with gadolinium indicates active MS lesions that may enhance for up to 2–6 weeks after an exacerbation.
- Evoked response potentials detect slow or abnormal conduction in response to visual, auditory, or somatosensory stimuli (**rarely used** because many other neurologic diseases can cause an abnormal result).
- CSF analysis usually reveals a mild pleocytosis (<50 cells/μL) and total protein that is mildly elevated.
- Elevated IgG index (oligoclonal bands) (up to 90% of patients) but is nonspecific, so CSF for oligoclonal banding recommended only when MRI is nonconfirmatory yet clinical suspicion for MS remains high.

Treatment. Treatment of MS can be divided into disease-modifying therapies, treatment of complications, and treatment for symptomatic relief during an acute exacerbation.

- **Disease-modifying therapies** (interferon β1a and β1b; glatiramer acetate [or copolymer I]) are used for relapsing-remitting disease to reduce the number of clinical exacerbations, decrease MRI activity, and delay the onset of significant disability.
  - For **primary** progressive disease: no approved disease-modifying treatment

Note

MS is an unusual disease in that the best initial test for diagnosis is also the most sensitive test, namely **MRI of the brain and spine**.

Note

In MS, protein >100 mg/dL is unusual and should be considered as evidence *against* the diagnosis of this condition.

Note

All disease-modifying therapies are relatively **contraindicated in pregnancy**. Interferon and glatiramer should both be stopped for a pregnancy.

  - For **secondary** progressive disease: interferon-β1b and mitoxantrone
    - Methotrexate, mitoxantrone, cyclophosphamide, IV immunoglobulin, or azathioprine if patients with relapsing-remitting or secondary progressive disease cannot tolerate interferon β1a/β1b or glatiramer acetate
      - Side effects of mitoxantrone include dose-related cardiotoxicity, so give only to those with normal ejection fraction.
      - Natalizumab is associated with progressive multifocal leukoencephalopathy.
      - Do not use mitoxantrone, cyclophosphamide, or natalizumab for a first episode of disease.
    - ACTH is no longer used.

- **Treatment of complications**
  - Glucocorticoids to reduce the length and intensity of an acute exacerbation
    - Give intense IV steroids for 3 days, followed by a course of oral medication tapered over 4 weeks
    - If no response and disease is severe, consider plasma exchange
  - Baclofen for spasticity (tizanidine and diazepam are helpful in nocturnal spasticity but are limited for daytime symptoms because they cause intense somnolence)
  - Carbamazepine, gabapentin, phenytoin, pregabalin, or tricyclic antidepressants for pain secondary to trigeminal neuralgia and dysesthesias
  - Oxybutynin for bladder hyperactivity
  - Bethanechol for urinary retention
  - Amantadine or fluoxetine for fatigue
  - Sildenafil acetate for erectile dysfunction

Note

Mitoxantrone is not first-line to prevent disease progression of MS because of its cardiotoxicity.

Fingolimod is an oral disease-modifying medication that decreases rates of MRI progression. It prevents lymphocytes from proliferating outside of lymph nodes. Cardiac toxicity can be severe.

Dalfampridine is an oral disease-modifying medication that increases walking speed. It is a unique potassium channel blocker for which the precise mechanism of action (for improved walking speed) is not clearly known.

Myasthenia Gravis

> A 35-year-old woman comes to the clinic complaining of double vision that seems to worsen near the end of the day. She also complains of difficulty chewing meat and other hard foods. Her symptoms seem to improve after a good night's sleep. On neurologic examination you note a snarling appearance when the patient is asked to smile, and a nasal tone is heard in her voice. You also note a weakness in the upper extremities when she is asked to clench her fist around your finger repeatedly.

Myasthenia gravis (MG) is a disease of the neuromuscular junction characterized by weakness and fatigability. In MG, an autoimmune process characterized by acetylcholine-receptor antibodies leads to a decreased number of active and functional acetylcholine receptors at the postsynaptic membrane.

Clinical Presentation. The major features in a patient's history that help to diagnose MG are muscle weakness and fatigability.

- **Early disease**: diplopia/ptosis/difficulty swallowing, speech with a "mushy" or nasal quality, facial weakness that manifests as a "snarl" when smiling
- **Later disease**: generalized weakness involving proximal muscles in an asymmetric pattern, intact deep tendon reflexes, normal pupillary responses, no sensory abnormalities
- **Very severe disease**: muscles of respiration

Diagnosis.

- Acetylcholine-receptor antibody test will be positive (close to 90% of patients).
  - In the presence of fatigable muscle weakness, a positive antibody test is specific and virtually diagnostic.
  - Antibodies are present in only 70% of those with disease limited to the eyes.
- Edrophonium (Tensilon) test is sensitive but not specific for diagnosis. Additionally, patients may experience nausea/diarrhea, fasciculations, syncope (rare), or bradycardia during the test, which are cholinergic symptoms.
- X-ray and CT of the chest to detect a thymoma (found in 10–15% of patients); thymic hyperplasia is found in 65% of patients
- Electromyography (EMG) is the most accurate test; a decremental decrease in muscle fiber contraction on repetitive nerve stimulation is the characteristic finding.

Treatment.

- Anticholinesterase medications such as pyridostigmine (**preferred**, as it is longer-lasting) or neostigmine
- If no response with anticholinesterase medications, consider thymectomy for patients who are postpubertal but age <60.
  - Thymectomy can prevent the use of potentially toxic medication such as systemic steroids.
  - Thymectomy can help to prevent the spread of malignancy thymic disease when a thymoma is present.
- If no response to anticholinesterase medications or thymectomy, consider immunosuppressive therapy to improve weakness.
  - Plasmapheresis and IV immunoglobulin have a rapid effect; reserve for those in acute myasthenic crisis
  - Glucocorticoids, but take 1–3 months for a clinical benefit
  - Steroids (initial immunosuppressive of choice); if no response, add azathioprine (take 3–6 months for a clinical benefit); alternatives to azathioprine are cyclosporine and cyclophosphamide, but they are more toxic.
  - Mycophenolate, a newer immunosuppressive drug that has fewer side effects than steroids or cyclophosphamide

Aminoglycoside antibiotics may exacerbate MG and should be avoided. (In fact, many medications may worsen MG.)

Note

Eaton-Lambert myasthenic syndrome (rare) is characterized by **increasing** muscle strength on repetitive contraction. It is associated with malignancy—especially small-cell carcinoma of the lung. Botulism may cause a myasthenic-like illness, but the pupils are usually dilated, and repetitive nerve stimulation (on EMG) shows an incremental increase in muscular fiber contraction (**opposite of MG**).

Clinical Recall

What is the best initial test in the diagnosis of myasthenia gravis?

A. Tensilon (Edrophonium) test

B. EMG

C. Chest CT

D. Acetylcholine receptor antibody test

E. Muscle biopsy

Answer: D

Guillain-Barré Syndrome

A 46-year-old man presents with "rubbery legs" for 2 days. He explains that the only other health issue has been several episodes of diarrhea 3 weeks ago, but those resolved spontaneously. On neurologic examination, bilateral lower-extremity weakness and a loss of reflexes are noted.

Guillain-Barré syndrome (GBS) is an acute, often severe polyradiculopathy, whose underlying pathophysiology is an autoimmune destruction of myelin. Evidence suggests that the etiology is a misdirection of the immune response, where the body's immune system attacks self-antigens mistaken for foreign antigens (molecular mimicry).

Approximately 75% of patients will have a history of an infection 1-3 weeks before the onset of symptoms, typically in the respiratory or GI system (*Campylobacter jejuni*). This might be an infection with human herpesvirus, cytomegalovirus, or Epstein-Barr.

The condition is seen more frequently in those with HIV, SLE, and lymphoma.

Clinical Presentation. Most patients present with rapidly developing weakness that typically begins in the lower extremities and moves upward. Symptoms will develop over hours to days, with the legs affected more often than the arms or face.

- Motor weakness
- Poor reflexes (in muscle groups affected)
- Sensory disturbances in the form of pain or tingling dysesthesia (due to loss of large sensory fibers, which leads to loss of reflexes and proprioception)
- Severe disease: autonomic instability (profuse sweating, postural hypotension, labile BP, cardiac dysrhythmias) requiring intensive care

Fever, constitutional symptoms, or bladder dysfunction are rare and should raise the possibility of alternate diagnoses.

Diagnosis lies principally in recognizing the typical pattern of weakness with the absence of reflexes, fever, and constitutional symptoms.

Note

The only association between immunizations and GBS occurred in 1976, with the introduction of the swine influenza vaccine. More recent formulations of influenza vaccine are associated with one case of GBS per million patients immunized.

- Lumbar puncture for protein and cell count is the best initial test.
- The characteristic finding is elevated protein without an associated rise in cell count on CSF (only seen 48 hours after the onset of symptoms).
- The most accurate test for diagnosis is electromyography (EMG), which can detect evidence of demyelination of the peripheral nerves.

Treatment is IV immunoglobulin or plasmapheresis (equally effective). There is no benefit to combination therapy.

- Treatment becomes ineffective about 2 weeks after the onset of symptoms, so initiate therapy immediately.
- Vital capacity must be monitored in those with GBS, and early respiratory support must be given to prevent death from respiratory failure.

Glucocorticoids are not effective for acute GBS.

MOVEMENT DISORDERS

Parkinson Disease

> A 56-year-old man is evaluated for a resting tremor that his wife noticed recently. She explains that her husband has been moving "very slowly" as of late. The patient says he feels fine and does not know why his wife is dragging him here. His past medical history is significant for mild hypertension that has been treated with a thiazide diuretic. Physical examination is significant for a resting tremor noted in the right hand. When walking, the patient is stooped forward, taking small steps. You note cogwheel rigidity in his right upper extremity with a positive Myerson sign.

Parkinson disease is a neurologic syndrome resulting from the deficiency of the neurotransmitter dopamine as a consequence of degenerative, vascular, or inflammatory changes in the basal ganglia. There are numerous causes.

- Drugs, including neuroleptic agents (haloperidol, chlorpromazine), antiemetics (metoclopramide), alpha-methyldopa, and reserpine
- Poisoning from MPTP, carbon monoxide, cyanide, and manganese
- Any structural lesion around the basal ganglia (trauma, tumor, abscess, infarct)
- Survivors of encephalitis can develop *postencephalitic Parkinsonism*.

Clinical Presentation. Cardinal symptoms are:

- Bradykinesia (manifested by slow movements, mask facies, reduction of automatic movements)
- Cogwheel rigidity
- Postural instability
- Resting tremor

Note

A useful mnemonic is to think of Mr. Parkinson as a fine **BRIT**ish gentleman.

- Bradykinesia
- Rigidity (cogwheel)
- Instability (postural)
- Tremor (resting)

Other diseases that can imitate Parkinsonism:

- **Severe depression** can cause a paucity of spontaneous movement that can mimic Parkinsonism.
- **Essential tremor** can be mistaken for the tremor of Parkinson disease, but the lack of other neurologic symptoms and a positive family history of tremor and its amelioration with alcohol distinguish them.
- A **normal pressure hydrocephalus** can present with ataxia and gait disturbances, which can be mistaken for Parkinson disease. The presence of dementia and urinary incontinence with dilated ventricles on head CT scan can help identify this disorder.
- **Huntington disease** can present with akinesia and chorea. The positive family history and dementia usually suggest the correct diagnosis.

Diagnosis. The diagnosis of Parkinson disease is a clinical one. Identify any secondary causes of a patient's Parkinsonism that are potentially reversible.

There are no diagnostic tests that can identify patients with Parkinson disease.

Treatment. The underlying pathophysiology causing Parkinson disease is the imbalance of dopaminergic (too little) and cholinergic (too much) tone on the basal ganglia. Thus, medical treatment revolves around increasing dopaminergic tone or decreasing cholinergic tone on the basal ganglia. Specifically, they do one of the following:

- Directly stimulate dopamine receptors (carbidopa/levodopa, dopamine agonists)
- Indirectly increase the amount of dopamine available (COMT inhibitors, selegiline, amantadine)
- Block acetylcholine stimulation of the basal ganglia (benztropine, trihexyphenidyl)

Direct-acting dopamine agonists such as pramipexole or ropinirole can be used alone as initial therapy or in combination with small doses of levodopa/carbidopa. Two other dopamine agonists are bromocriptine and cabergoline. All of them are less effective than levodopa.

Dopamine agonists have fewer dyskinetic side effects. Bromocriptine and pergolide are ergot derivatives and can cause cardiac toxicity.

The first step when considering which medication to start with is evaluating the patient's functional status.

- **Intact functional status** (less bradykinesia)
  - Age <60: anticholinergic medication, particularly when tremor is predominant symptom
  - Age >60: amantadine (because side effects of anticholinergics are relatively contraindicated in the elderly, e.g., dry mouth, urinary retention, constipation, confusion/hallucinations)
  - Anticholinergics, e.g., benztropine and trihexyphenidyl, to relieve tremor and rigidity (avoid with BPH and glaucoma)

Clinical Correlate

There are a number of "Parkinson plus" syndromes, which are characterized by their relative lack of response to therapy with levodopa/carbidopa.

- Parkinsonism + vertical gaze palsy = **supranuclear palsy**
- Parkinsonism + prominent ataxia = **olivopontocerebellar atrophy**
- Parkinsonism + prominent orthostatic hypotension = **multiple-system atrophy** (previously called Shy-Drager syndrome)

Note

For those Parkinson's patients whose functional status is intact, treatment does not start with carbidopa/levodopa.

- **Compromised functional status** (more significant bradykinesia)
  - Carbidopa/levodopa (**best initial therapy**) to inhibit extracerebral dopa-decarboxylase, allowing more of the levodopa to reach the CNS, where it is needed.
    - Levodopa is the precursor to dopamine.
    - Carbidopa protects the levodopa from breakdown in the periphery, ensuring its secure delivery to the CNS.
    - Late complications to carbidopa/levodopa therapy include dyskinesia (abnormal movements), akathisia (restlessness), and "on-off" phenomena (all are called "response fluctuations"); management is a sustained release form of carbidopa/levodopa plus a dopamine agonist, selegiline, or COMT inhibitor (tolcapone or entacapone), or restricting the main protein meal to the night.

Selegiline, which was once thought to slow progression of the disease, can offer mild symptomatic benefit in early disease. It can be used when there is a declining or fluctuating response to levodopa. Rasagiline is a newer version.

When there is no response to medical therapy, surgery is a last resort, i.e., pallidotomy, thalamotomy, or placement of deep brain stimulators in the globus pallidus or subthalamic nuclei.

Note

COMT inhibitors have no effect alone. Always use in conjunction with levodopa to help reduce side effects.

Huntington Disease

> A 34-year-old man presents for an evaluation of strange spontaneous movements he has been having. Recently, while sitting at a family dinner, he experienced uncontrolled grimacing with grunting. His father died at age 41 from "dementia."

Huntington disease is a genetic degenerative brain disorder caused by the presence of the HD gene located on chromosome 4p. The gene contains a CAG trinucleotide repeat expansion that codes for a protein called *huntingtin*. The HD mutation leads to abnormal cleavage of the huntingtin protein, interfering with nuclear mechanisms and causing cell death.

The disease is inherited in an autosomal dominant fashion. Successive generations tend to have the disease occurring at an earlier age. This is called *anticipation*.

Clinical hallmarks of the disease include chorea and behavioral disturbance. Onset is usually in decade 4 or 5 of life, and can begin with chorea or behavioral change.

- Chorea changes may begin as fidgeting that progresses to sudden movements of the trunk or limbs. Gait is poorly coordinated and has a choreic quality. Memory is usually preserved until late in the disease, but lack of judgment, disinhibition, and inattention are early manifestations. There is frequently an associated depression. Dementia becomes severe later in the disease.
- Behavioral (personality) changes consist of irritability, anger, paranoia, depression, and even antisocial behavior.

Diagnosis is made by genetically testing for the presence of the CAG trinucleotide DNA repeat expansion. There is a 50% chance of passing it on to children. CT scanning shows cerebral atrophy. Atrophy of the caudate nucleus is severe later.

Treatment is tetrabenazine to help the movement disorder of Huntington (but it will not reverse or cure the underlying disease process). Death occurs 15–20 years after the diagnosis. Haloperidol or clozapine can be used to control behavioral changes.

Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is an idiopathic disorder of both upper and lower motor neurons. The disease has a unique presentation. Symptoms include muscle weakness plus upper motor neuron loss, cranial nerve palsies, respiratory involvement, and lower motor neuron destruction. At the same time, bowel, bladder sensory, cognitive, and sexual function are preserved.

- Dysphagia, difficulty chewing, decreased gag reflex, dysarthria (difficulty in articulating words), and difficulty in handling saliva, due to the cranial nerve, or bulbar, palsies
- Recurrent aspiration pneumonia (**most common cause of death**) due to respiratory muscle involvement
- Weak cough (**common**), which only worsens the respiratory problem
- Head ptosis due to the extensor muscles of the neck becoming too weak to keep the head up
- Significant spasticity that can lead to pain, due to the upper motor neuron involvement
- Both upper and lower motor neuron weakness (**hallmark sign**)
  - Upper motor neuron manifestations: weakness with spasticity and hyperreflexia
  - Lower motor neuron manifestations: weakness with muscle wasting, atrophy, and fasciculations, including tongue atrophy
- The most accurate confirmatory test is the electromyogram, which will show diffuse axonal disease. CPK levels are sometimes mildly elevated, and the cerebrospinal fluid and MRI scans are normal.

This is entirely a motor neuron disease, so there is no pain from abnormal sensory neuropathy. Mentation, bowel, bladder, and sexual function remain intact for the same reason. In other words, a fully mentally alert patient loses nearly all motor control while still being able to think and perceive. The patient becomes fully aware of being trapped in a body that does not function.

Treatment. The only treatment that may slow down progression of the disease is riluzole, which is inhibits glutamate release. Death typically results in 3–5 years. Spasticity is treated with baclofen and tizanidine.

Many of the exam questions regarding ALS will be **ethical questions on issues of the withholding of care**. Since ALS has no impact on cognitive function, the patient is felt to retain the capacity to make medical decisions.

- The patient has the right to refuse potentially life-saving therapy such as antibiotics, nasogastric tube placement, tracheostomy, or mechanical ventilation.
- The patient should not be allowed to commit suicide nor should the physician assist with suicide. (Withholding intubation or antibiotics is not considered assisting a suicide.)
- Every adult patient with the capacity to understand the implications of his or her choice is allowed to refuse any unwanted therapy.

Restless Leg Syndrome

Restless leg syndrome (RLS) is an idiopathic condition resulting in a sensation of creeping and crawling dysesthesia within the legs, leading to involuntary movements during sleep. Often the condition is brought to attention because of multiple bruises sustained by the sleep partner. The condition can be familial and is exacerbated by sleep deprivation, caffeine, and pregnancy. There is also an association with uremia, iron deficiency, and peripheral neuropathy.

There is no specific diagnostic test for this disorder. Treatment is a dopamine agonist such as pramipexole or ropinirole, although some patients may need levodopa/carbidopa. Other therapies are narcotics and benzodiazepines.

Clinical Recall

Which of the following is a characteristic feature of Creutzfeldt-Jakob disease?

A. Memory loss without dysfunction of other cognitive domains

B. Gradual loss of memory with other cognitive disturbances

C. Memory impairment with social, interpersonal, and emotional problems

D. Stepwise progression of cognitive decline

E. Rapidly progressive dementia with myoclonic jerks

Answer: E

Benign Essential Tremor

Benign essential tremor is an idiopathic disorder of an isolated tremor in the hands or head (or both). The lower extremities tend to be spared.

- Worsened with caffeine or beta agonists
- Improves with alcohol (**characteristic sign**); patients describe shaky hands that improve with 2–3 drinks
- Examination reveals no other abnormalities
- Manual skills such as the ability to write may be affected (but level of disability is limited)

There is no specific diagnostic test for this disorder.

Treatment is propranolol. If no response, try primidone, alprazolam, and clozapine.

If still no response, consider thalamotomy.

Dermatology 12

Learning Objectives

- Describe the mechanism of bullous and blistering diseases and approaches to treatment
- List the common dermatologic parasitic diseases, treatments, and common side effects
- Outline the treatment of skin and ulcer infections, including decubitus (pressure) ulcers and acne
- Describe the presentation and management of scalp, hair, and scaling disorders (eczema), and papulosquamous dermatitis
- Provide an overview of toxin-mediated diseases, hypersensitivity, and toxin-mediated diseases
- Describe benign lesions, precancerous lesions, and malignant diseases of the skin and their treatment and prognosis

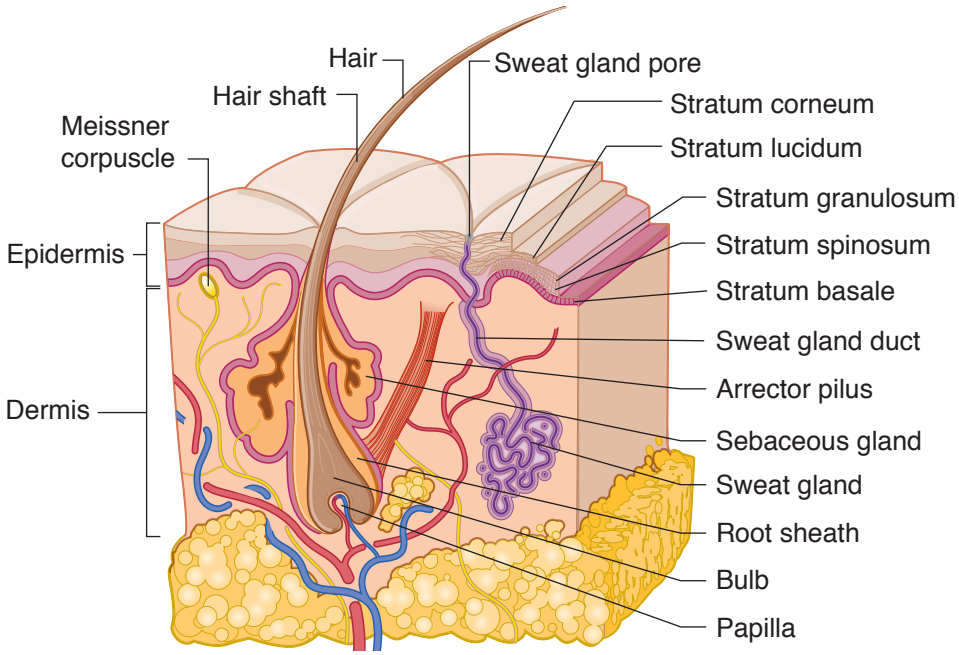


Figure 12-1. Skin

BULLOUS/BLISTERING DISEASES

Pemphigus Vulgaris

Pemphigus vulgaris is an autoimmune disease of unclear etiology in which the body essentially becomes allergic to its own skin. Antibodies are produced against antigens in the intercellular spaces of the epidermal cells. They attack the "glue" that holds the epidermal cells together. Pemphigus vulgaris is most often idiopathic, but ACE inhibitors or penicillamine can occasionally cause it.

- Seen in decades 3-4
- Occurs prominently in the mouth and starts there
- Oral lesions are erosions, not bullae.
- The bullae are very thin and flaccid and can break easily, causing loss of large volumes of skin surface area and acting like a burn. (This is because the bullae occur from destruction within the epidermis, making them thinner and more fragile.)
- Presence of the **Nikolsky sign** (the easy removal of skin by just a little pressure from the examiner's finger, pulling the skin off like a sheet) is seen in pemphigus vulgaris, staphylococcal scalded skin syndrome, and toxic epidermal necrolysis.
- Lesions are painful, not pruritic.

The most accurate diagnostic test is to biopsy the skin and to use immunofluorescent stains, which will detect intercellular deposits of IgG and C3 in the epidermis.

Treatment.

- Systemic glucocorticoids, such as prednisone (topical steroids are not strong enough)
- When no response with steroids, use azathioprine, mycophenolate, or cyclophosphamide
- Rituximab and IVIG are also effective.

Bullous Pemphigoid

Pemphigoid is 2× as common as pemphigus vulgaris and occurs in elderly persons age 70s and 80s. It can also be drug-induced with sulfa drugs, including furosemide, penicillamine, and others.

The defect occurs at the **dermo-epidermal junction**, so the layer of skin that separates off is much thicker. Because the fracture of the skin causing the blisters is deeper, the bullae are thicker walled and much less likely to rupture. Oral lesions are rare. Because the bullae are tense and intact, the skin is better protected. There is no dressing for skin as good as skin itself. Hence, there is much less fluid loss, and infection is much less likely as compared with pemphigus vulgaris. Mortality is much less likely in bullous pemphigoid.

The most accurate diagnostic test is a biopsy with immunofluorescent antibodies at the dermo-epidermal junction (basement membrane).

Systemic steroids, such as prednisone, are the standard means of treatment. Tetracycline or erythromycin combined with nicotinamide is the alternative to steroids. Use topical steroids only if no oral lesions are present.

Note

"Pemphix" is from the Greek word for bubble, which is what a bulla looks like before it is broken.

Note

Pemphigus vulgaris is a much more serious and potentially life-threatening disease than pemphigoid.

Note

The **Nikolsky sign** (easy removal of skin with a little pressure from the examiner's finger, pulling the skin off like a sheet) is seen in pemphigus vulgaris, staphylococcal scalded skin syndrome, and TEN.

Note

Before the invention of steroids, pemphigus vulgaris was often fatal, with patients dying of sepsis and dehydration–just like a burn patient.

Porphyria Cutanea Tarda

Porphyria cutanea tarda is a disorder of porphyrin metabolism. Deficiency of the enzyme uroporphyrinogen decarboxylase results in an abnormally high accumulation of porphyrins, which then leads to a photosensitivity reaction.

On the exam, the patient may have a history of HIV, liver disease, or chronic hepatitis C, or may be taking oral contraceptives. The liver disease may be from any cause but is most likely to involve chronic infectious hepatitis or hemochromatosis, because porphyria cutanea tarda is associated with increased liver iron stores. Diabetes is found in 25% of patients.

Clinical Presentation. Fragile, nonhealing blisters are seen on the *sun-exposed* parts of the body, such as the backs of the hands and the face. This leads to hyperpigmentation of the skin in general and hypertrichosis of the face.

Diagnosis. The diagnostic test is a level of urinary uroporphyrins. Uroporphyrins are elevated 2–5× above the coproporphyrins in this disease.

Treatment.

- Stop alcohol intake and discontinue estrogen use
- Add sun protection, including protective clothing, because most sunscreens do not seem to block the wavelength of light causing the dermal reaction
- If no response, consider phlebotomy to remove iron
- Deferoxamine if phlebotomy is not possible
- Chloroquine to increase excretion of porphyrins

DRUG ERUPTIONS/HYPERSENSITIVITY

Urticaria

Acute urticaria is a hypersensitivity reaction most often mediated by IgE and mast cell activation, resulting in evanescent wheals and hives. It is a type of localized, cutaneous anaphylaxis, but without the hypotension and hemodynamic instability. The most common causes of acute urticaria are allergic reactions to medications, insect bites, and foods, and occasionally, the result of emotions. The most common medications are aspirin, NSAIDs, morphine, codeine, penicillins, phenytoin, and quinolones. ACE inhibitors are also associated with urticaria, as well as angioedema. The most common foods are peanuts, shellfish, tomatoes, and strawberries. Contact with latex in any form can also cause urticaria.

Clinical Presentation. Itching is prominent.

- **Acute urticaria** lasts <6 weeks, and 70% of cases are self-limited. Wheals and hives are seen within 30 minutes and last <24 hours.
- **Chronic urticaria** lasts >6 weeks, and is associated with pressure on the skin, cold, or vibration. If >6 weeks, investigate the etiology.

Note

Pressure on the skin resulting in localized urticaria is also known as dermatographism.

Note

For urticaria, **never use astemizole or terfenadine** (no longer marketed), as they can cause potentially fatal rhythm disturbances.

Note

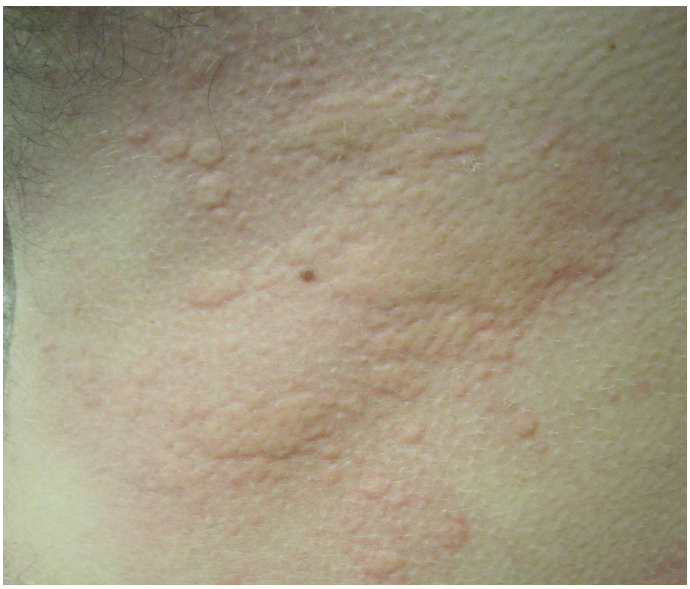
For urticaria:

Answer "**terfenadine**" or "astemizole" only when the test question asks what will kill the patient or which is the most dangerous medication.

Answer "**desensitization**" when the trigger cannot be avoided, e.g., a beesting in a farmer. Beta blocker medications must be stopped prior to desensitization because they inhibit epinephrine, which may be used if there is an anaphylactic reaction.

Treatment. Urticaria is treated with H_1 antihistamines.

- **Severe, acute urticaria**: older medications, such as diphenhydramine, hydroxyzine, or cyproheptadine; if life-threatening, use H_2 antihistamines when H_1 antihistamines fail and add systemic steroids
- **Chronic urticaria**: newer, nonsedating antihistamines, such loratadine, desloratadine, fexofenadine, or cetirizine



Wikipedia, James Heilman, MD

Figure 12-2. Urticaria

Morbilliform Rashes

A morbilliform rash is a milder version of a hypersensitivity reaction compared with urticaria. This is the "typical" type of drug reaction and is lymphocyte mediated.

The rash resembles measles and is usually secondary to medications that the patient is allergic to, such as penicillin, sulfa drugs, allopurinol, or phenytoin. It is a generalized, maculopapular eruption that blanches with pressure. The reaction can appear a few days after the exposure and may begin even after the medication has been stopped.

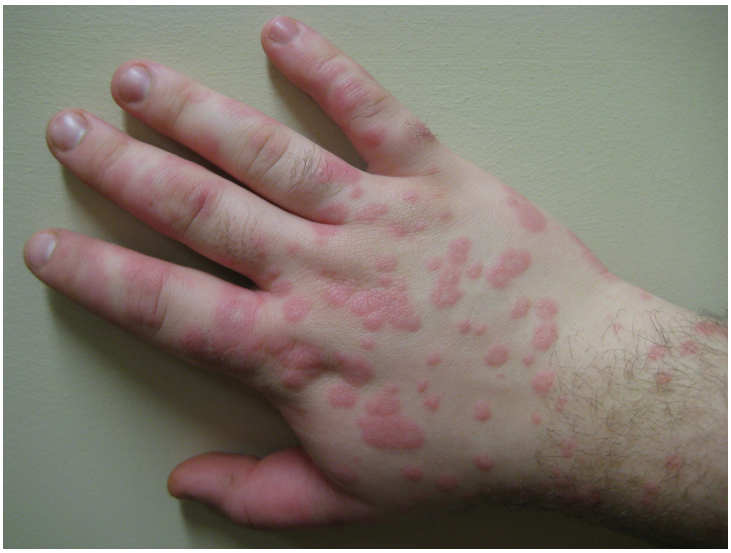
Antihistamines are effective, and steroids are rarely necessary.

Erythema Multiforme

Although erythema multiforme (EM) may be caused by the same types of medications that cause urticaria and morbilliform rashes (penicillins, phenytoin, NSAIDs, and sulfa drugs), the most common cause of EM is a reaction to infection. The majority of cases follow infection with herpes simplex or *Mycoplasma*.

The most characteristic feature of EM is target-like lesions that occur especially on the palms and soles. These lesions can also be described as "iris-like." Bullae are not uniformly found. EM of this type usually does not involve mucous membranes.

Treatment is antihistamines and treatment of the underlying infection.



Wikipedia, James Heilman, MD

Figure 12-3. Erythema Multiforme

Stevens-Johnson Syndrome

Stevens-Johnson syndrome (SJS) (sometimes called *erythema multiforme major*) can be difficult to distinguish from toxic epidermal necrolysis (TEN) and, in fact, the two diseases may be considered a spectrum of severity of the same disorder.

All of these disorders may arise as a hypersensitivity response to the same set of medications, such as penicillins, sulfa drugs, NSAIDs, phenytoin, and phenobarbital.

Clinical Presentation.

- Involves <10–15% of total body surface area
- Overall mortality rate <5–10%
- Mucous-membrane involvement in 90% of cases; most often the oral cavity and conjunctivae, but frequently the respiratory tract

Treatment is early admission to a burn unit, withdrawal of the offending drug, and supportive care. Respiratory tract involvement may be so severe as to require mechanical ventilation. Death occurs from a combination of infection, dehydration, and malnutrition.

For severe disease, the best initial therapy is IV immunoglobulins. Other therapies of unclear value are cyclophosphamide, cyclosporine, and thalidomide.

There is no proven benefit for steroids.

Toxic Epidermal Necrolysis

Toxic epidermal necrolysis (TEN) is the most serious version of a cutaneous hypersensitivity reaction. Mortality may be 40–50%.

- Involves 30–100% of total body surface area
- Nikolsky sign is present, and the skin easily sloughs off
- Has some features similar to staphylococcal scalded skin syndrome, but is drug-induced and not caused by a toxin coming from an organism

Diagnosis of TEN is usually clinical. The most accurate diagnostic test is a skin biopsy, which will reveal full thickness epidermal necrosis. Skin biopsy is usually not necessary.

Treatment. Sepsis is the most common cause of death, but prophylactic systemic antibiotics are not indicated. Systemic steroids are not effective and may, in fact, decrease survival.

Fixed Drug Reaction

Fixed drug reaction is a **localized** allergic drug reaction that recurs at precisely the **same anatomic site** on the skin with repeated drug exposure. It is not known why the reactions are anatomically localized and do not become generalized morbilliform rashes. The most commonly implicated drugs include aspirin, NSAIDs, tetracycline, and barbiturates.

Fixed drug reactions are generally round, sharply demarcated lesions that leave a hyperpigmented spot at the site after they resolve.

Discontinue the offending drug, and treat the reactions with topical steroids.

Clinical Pearl

Always do a chest x-ray on a patient with EN, to exclude sarcoidosis.

A biopsy of EN lesions will show nonspecific inflammation.

Erythema Nodosum

Erythema nodosum (EN) is a localized inflammatory condition of the skin or panniculitis. It is secondary to recent infections or inflammatory conditions. It is also associated with pregnancy. The most common causes of EN are recent streptococcal infections, coccidioidomycoses, histoplasmosis, sarcoidosis, inflammatory bowel disease, syphilis, TB, and hepatitis. Enteric infections such as *Yersinia* also cause the disorder.

EN consists of multiple painful, red, raised nodules on the anterior surface of the lower extremities. They are extremely tender to palpation. They do not ulcerate, and they generally last about 6 weeks.

Diagnosis. ASLO titers can help determine who has recently had a streptococcal infection if there is no other etiology apparent from the history.

Treat the underlying disease and use analgesics and NSAIDs. Potassium iodide solution can be used when patients do not respond to symptomatic therapy. EN is usually a self-limiting condition.

Clinical Recall

A 23-year-old woman from Bangladesh presents with seizure disorders. Prior to initiating treatment, which of the following should you check to avoid Stevens-Johnson syndrome?

A. HLA-B27

B. HLA-B57

C. HLA-B1502

D. HLA-B5801

Answer: C

INFECTIONS

Fungal Infections

Tinea pedis, cruris, corporis, versicolor, capitis, and onychomycosis

All of the superficial fungal infections of the body share a number of common characteristics leading to the same answer on the test for similar questions for each of these diseases. "Superficial fungal infections" refer to those infections limited to the skin, nails, and hair. Remember, though, that these answers would not be valid for more deep-seated, life-threatening infections, such as fungal endocarditis, meningitis, or abscesses.

Clinical Presentation and Diagnosis. All superficial fungal infections of the skin, hair, and nails are primarily diagnosed by their *visual appearance* and confirmed by a potassium hydroxide *(KOH) test* of the skin. The leading edge of the lesion on the skin or nails is scraped with a scalpel to remove some of the epithelial cells or some of the nail and hair. KOH has the ability to dissolve the epithelial cells and collagen of the nail, but does not have the ability to melt away the fungus. Hence, a KOH preparation gives an immediate diagnostic answer by revealing fungal hyphae. This is particularly characteristic in tinea versicolor, where the *Malassezia furfur (Pityrosporum orbiculare)* organism appears in a "spaghetti and meatballs" pattern.

The most accurate test is to culture the fungus. This is usually not clinically practical because molds that grow on the skin (dermatophytes) take up to 6 weeks to grow even on specialized fungal media. A specific species usually does not need to be isolated in most cases, unless it is an infection of the hair or nails. In the case of nail and hair infections, oral therapy is necessary, and it is important to be precise because there are fewer medications that can be used to effectively treat onychomycosis. Tinea tonsurans is the cause of >90% of cases of tinea capitis.

Treatment. For onychomycosis (nail infection) or hair infection (tinea capitis), the medications with the greatest efficacy are oral terbinafine or itraconazole. These medications are used for at least 6 weeks for fingernails and 12 weeks for toenails. Terbinafine is potentially hepatotoxic, and it is important to periodically check liver function tests. Griseofulvin must be used for 6 to 12 months in the treatment of fingernails and has much less antifungal efficacy than terbinafine. Griseofulvin is no longer recommended in the treatment of onychomycosis of the toenails. In the treatment of tinea capitis, griseofulvin is recommended for 6 to 8 weeks.

Note

Drug of choice for oral antifungal treatment:

- Tinea capitis and onychomycosis
  - Terbinafine or itraconazole

The other fungal infections of the skin that don't involve hair or nails may be treated with any of the following topical medications: ketoconazole, clotrimazole, econazole, terbinafine, miconazole, sertaconazole, sulconazole, tolnaftate, or naftifine. There is no clear difference in efficacy or adverse effects between them when used topically. Ketoconazole has more adverse effects when used systemically, such as hepatotoxicity and gynecomastia. This is why ketoconazole is not a good choice for onychomycosis. There is no topical form of fluconazole. Fluconazole is also less efficacious for dermatophytes of the nails when used systemically.

Antifungal medications generally should not be used in combination with topical steroids, unless a diagnosis has been confirmed. Steroids in a cream can relieve redness and itching and give the appearance of improvement even in impetigo and contact dermatitis.

Tinea versicolor

Tinea versicolor is a skin infection characterized by multiple macules (usually asymptomatic), varying in color from white to brown. It is caused by *Pityrosporum orbiculare* (*Malassezia furfur*).

Clinical Correlate

Tinea versicolor has some additional features that are important in its management. It presents with lesions of different colors from tan to pink (hence the name *versi*color). The lesions often do not tan, and they present with pale areas in the middle of a normal tan. This can be distinguished from vitiligo by the fact that vitiligo has *no* pigmentation, whereas tinea versicolor presents with *altered* pigmentation. The organism may also be contagious. A KOH preparation and fungal culture are used in the same manner as for the other dermatophytes. The main therapeutic difference is the use of topical selenium sulfide every 2 to 3 weeks versus oral therapy with itraconazole or fluconazole. This is not because of antifungal resistance; it is because tinea versicolor is much more likely to involve large amounts of body surface area so it is difficult to cover this volume of skin with an ordinary topical cream or lotion.

Clinical Presentation. Tan, brown, or white scaling macular lesions that tend to coalesce; found on chest, neck, abdomen, or face. Lesions do not tan.

Diagnosis. Skin scrapings examined with 10% KOH under a microscope. The classic description is of "spaghetti and meatballs," which refers to the hyphae and spores that can be seen in the KOH prep.

Treat with topical selenium sulfide, clotrimazole, ketoconazole, or oral itraconazole. Consider local or systemic therapy based on the amount of surface area involved.

Candidiasis

Candidiasis is a yeast infection usually involving skin and mucous membranes, but it can also be systemic. It is caused by *Candida albicans*. It usually spreads in patients with decreased host defenses, i.e., those with increased susceptibility due to systemic antibacterial therapy, obesity, DM, corticosteroid or antimetabolite therapy, pregnancy, debilitating disease and blood dyscrasias, or HIV.

Clinical Presentation

- Intertriginous infection: well-demarcated, erythematous, itchy, exudative patches, usually rimmed with small red-based pustules that occur in the groin, gluteal folds (diaper rash), axilla, umbilicus, and inframammary areas
- Vulvovaginitis: white or yellowish discharge with inflammation of the vaginal wall and vulva common in pregnant women and patients with DM
- Oral candidiasis (thrush): white patches of exudates on tongue or buccal mucosa
- Candidal paronychia: painful red swelling around the nail

Diagnosis. Potassium hydroxide on slide to visualize fungal forms. Culture is definitive.

Treatment

- Topical nystatin, clotrimazole, miconazole, ciclopirox, econazole, or terconazole
- Systemic amphotericin in serious invasive infections. Fluconazole in less serious infections. *Candida paronychia* requires systemic therapy.

Bacterial Infections

Antistaphylococcal antibiotics

The most common bacterial organisms to cause skin infections of any kind are *Staphylococcus* and *Streptococcus*. Antibiotics used to treat *Staphylococcus* are dicloxacillin, cephalexin (Keflex™), or cefadroxil (Duricef™). Cefadroxil, cefazolin, or cephalexin are the preferred agents. If a patient is allergic to penicillin, but the reaction is only a rash, then cephalosporins can be safely used. There is far less than 5% cross-reaction between penicillins and cephalosporins. The IV equivalents of oral dicloxacillin include oxacillin and nafcillin. The IV equivalent of cefadroxil is cefazolin.

If the penicillin reaction is anaphylaxis then cephalosporins cannot be used. The alternative antibiotics that will treat the skin are macrolides, such as erythromycin, azithromycin, clarithromycin, or the newer fluoroquinolones (levofloxacin or moxifloxacin). Ciprofloxacin will not adequately cover the skin. Vancomycin is only for IV use for skin infections, and oral vancomycin is not absorbed. Oral therapy for MRSA is with clindamycin, TMP/SMX, or doxycycline. The ultimate form of oral MRSA therapy is linezolid.

Impetigo

Impetigo is a superficial, pustular skin infection, seen mainly in children (ecthyma is an ulcerative form of impetigo), with oozing, crusting, and draining of the lesions. It is a superficial bacterial infection of the skin largely limited to the epidermis and not spreading below the dermal-epidermal junction. It is caused by group A beta-hemolytic *Streptococcus* and *S. aureus* (*bullous impetigo*).

- Because it is limited to the epidermis, the purulent material is easily able to express itself through the surface; therefore, the patient history will describe the infection with words such as "weeping," "oozing," "honey colored," or "draining."
- Occurs more often in warm, humid conditions, particularly when there is poverty and crowding of children. This is because it is both contagious and autoinoculable.

- More common on arms, legs, and face
- May follow trauma to skin
- Begins as maculopapules and rapidly progresses to vesicular pustular lesions or bullae. The crusts are described as having a golden or yellow appearance and if untreated can progress to lymphangitis, furunculosis, or cellulitis, and acute glomerulonephritis.
- May cause glomerulonephritis, but it will not cause rheumatic fever

Note

Group A *streptococci* and *S. aureus* are the most common causes of impetigo.

Treatment

- Oral first-generation cephalosporin or semisynthetic penicillin, e.g., oxacillin, cloxacillin, dicloxacillin (for severe or widespread cases)
- Topical mupirocin, bacitracin, or retapamulin for mild cases of impetigo
- Penicillin-allergic patients can be treated with macrolides such as clarithromycin or azithromycin.
- TMP/SMZ, clindamycin, or doxycycline for MRSA

Note

Retapamulin is a topical antibacterial that is more active against staph and strep than mupirocin or bacitracin.

Erysipelas

Erysipelas is a bacterial infection of a deeper layer of the skin than impetigo. Erysipelas involves both the dermis and epidermis and is most commonly caused by group A *Streptococcus* (*pyogenes*).

- Because it involves lymphatic channels in the dermis, erysipelas is more likely to result in fever, chills, and bacteremia.
- Often involves the face, giving a bright red, angry, swollen appearance
- Usually bilateral, shiny red, indurated edematous tender lesions on the face, arms, and legs
- Lesions often sharply demarcated from the surrounding normal skin
- Differentiate from herpes, contact dermatitis, and angioneurotic edema

Treatment. Semisynthetic penicillin or first-generation cephalosporin if you cannot distinguish it from cellulitis; penicillin (if *Streptococcus* is certain).

Cellulitis

Cellulitis is a bacterial infection of the dermis and subcutaneous tissues with *Staphylococcus* and *Streptococcus*. Cellulitis is characterized by redness, swelling, and warmth and tenderness of the skin. Because it is **below the dermal-epidermal junction**, there is no oozing, crusting, weeping, or draining.

Treatment. Cellulitis is treated with the antibiotics prescribed for erysipelas on the basis of the severity of the disease. If there is fever, hypotension, or signs of sepsis or if oral therapy has not been effective, then the patient should receive IV therapy. Oxacillin, nafcillin, or cefazolin is the best therapy. Treatment is generally empiric because injecting and aspirating sterile saline for a specific microbiologic diagnosis has only a 20% sensitivity. Oral therapy for MRSA is with clindamycin, TMP/SMX, or doxycycline.

Folliculitis, furuncles, and carbuncles

Folliculitis, furuncles, and carbuncles represent 3 degrees of severity of staphylococcal infections occurring around a hair follicle. Occasionally, folliculitis can be the result of those who contract *Pseudomonas* in a whirlpool or from a hot tub.

As folliculitis worsens from a simple superficial infection around a hair follicle, it becomes a small collection of infected material known as a furuncle. When several furuncles become confluent into a single lesion, the lesion becomes known as a carbuncle, which is essentially a localized skin abscess. Folliculitis is rarely tender, but furuncles and carbuncles are often extremely tender.

Treatment. Folliculitis mainly can be treated with warm compresses locally without the need for antibiotics. If antibiotics are required, mupirocin is the best choice. Furuncles and carbuncles require treatment with systemic antistaphylococcal antibiotics, and in the case of carbuncles, should be administered intravenously. Treatment with dicloxacillin, cephalexin, or cefadroxil is acceptable. A large furuncle or carbuncle will also require surgical drainage.

Necrotizing fasciitis

Necrotizing fasciitis is an extremely severe, life-threatening infection of the skin. It starts as a cellulitis that dissects into the fascial planes of the skin. *Streptococcus* and *Clostridium* are the most common organisms because they are able to produce a toxin that further worsens the damage to the fascia. Diabetes increases the risk of developing fasciitis.

The features which distinguish necrotizing fasciitis from simple cellulitis are a **very high fever**, a portal of entry into the skin, pain out of proportion to the superficial appearance, the presence of **bullae**, and **palpable crepitus**.

Laboratory evidence of necrotizing fasciitis is an elevated creatine phosphokinase and an x-ray, CT, or MRI that show **air in the tissue or necrosis**. All of these lab methods of establishing a diagnosis lack both sensitivity and specificity. Surgical debridement is the best way to confirm the diagnosis and is also the mainstay of therapy.

Treatment. Surgery is the mainstay of therapy. The best empiric antibiotics are the beta-lactam/beta-lactamase combination medications such as ampicillin/sulbactam (Unasyn™), ticarcillin/clavulanate (Timentin™), or piperacillin/tazobactam (Zosyn™). If there is a definite diagnosis of group A *Streptococcus (pyogenes)*, then treat with clindamycin and penicillin. Without adequate therapy, necrotizing fasciitis has an 80% mortality rate.

Paronychia

Paronychia is an infection loculated under the skin surrounding a *nail*. It is generally treated with a small incision to allow drainage and with antistaphylococcal antibiotics. The antistaphylococcal antibiotics are dicloxacillin, cefadroxil, or cephalexin orally, or oxacillin, nafcillin, or cefazolin intravenously.

Clinical Pearl

Necrotizing fasciitis is commonly associated with varicella infection, where the skin lesions are infected by *Streptococcus* or *Staph*.

Note

If an exam question presents an obvious clinical case with crepitus, pain, high fever, and a portal of entry, you should answer "surgery" (not a test, such as an x-ray) as the best initial step.

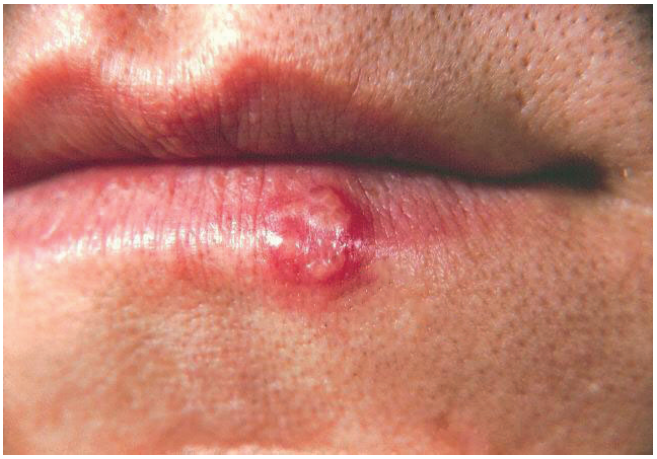
Viral Infections

Herpes simplex

Herpes simplex infections of the genitals are characterized by multiple, painful vesicles. The vesicles are usually obvious by examination, and antibiotic therapy should be initiated immediately without waiting for results of the tests.

Diagnosis is made with the **direct fluorescent antibody (DFA)** test or **HSV PCR**. Tzanck test and culture are no longer used. Serology is not useful for diagnosing herpes infections.

Immediate therapy is with oral acyclovir, famciclovir, or valacyclovir. Topical acyclovir has extremely little efficacy; it will slightly improve resolution in primary lesions and will do absolutely nothing for recurrent herpes simplex lesions. Topical penciclovir has some use for oral herpetic lesions, but it must be applied every 2 hours. The treatment of acyclovir-resistant herpes is with foscarnet.



Centers for Disease Control and Prevention

Figure 12-4. Herpes Simplex Lip

Herpes zoster/varicella

Chickenpox is primarily a disease of children. Complications of varicella are pneumonia, hepatitis, and dissemination. Episodes of dermatomal herpes zoster, also known as shingles, occur more frequently in the elderly and in those with defects of the lymphocytic portion of the immune system (i.e., leukemia, lymphoma, HIV, or those on steroids).

The vesicles are 2–3 mm in size at all stages of development and are on an erythematous base.

Diagnosis. Diagnostic testing is generally not necessary because little else will produce a band of vesicles in a dermatomal distribution besides herpes zoster.

Treatment. Chickenpox is generally not treated with antivirals. If the child is immunocompromised or the primary infection occurs in an adult, then acyclovir, valacyclovir, or famciclovir should be given.

Steroid use is still not clearly beneficial, although the best evidence for efficacy is in elderly patients with severe pain. The rapid administration of acyclovir still has the best efficacy for decreasing the risk of postherpetic neuralgia.

Other treatments for managing the pain are gabapentin, tricyclic antidepressants, and topical capsaicin. The most effective analgesic specific for postherpetic neuralgia is gabapentin. Nonimmune adults exposed to chickenpox should receive varicella zoster immunoglobulin within 96 hours of the exposure in order for it to be effective.

Molluscum contagiosum

Molluscum contagiosum is skin-colored, waxy, umbilicated papules. It is caused by poxvirus. It is commonly seen in children; frequency is increased in patients infected with HIV.

Small papules appear anywhere on the skin (genital and pubic area), usually by venereal contact, and are asymptomatic. The lesions have a central umbilication. They can be transmitted by skin-to-skin contact or sexually.

Diagnosis is made mainly on appearance. Lab testing is rarely, if ever, necessary. Giemsa stain will show large cells with inclusion bodies.

Treat with freezing, curettage, electrocautery, or cantharidin.

Clinical Recall

What is the most appropriate management for onychomycosis of the toenails?

A. PO griseofulvin

B. PO terbinafine

C. Topical itraconazole

D. PO griseofulvin and topical corticosteroids

E. Topical itraconazole and PO corticosteroids

Answer: B

PARASITIC INFECTIONS

Scabies

Scabies is a parasitic skin infection characterized by superficial burrows, intense pruritus, and secondary infections. It involves vesicular eruptions resulting from the females of the *Sarcoptes scabiei (hominis)* burrowing into the skin. It is caused by the itch mite *Sarcoptes scabiei*. Transmission is by skin-to-skin contact.

Scabies primarily involves the web spaces of the hands and feet. It also produces pruritic lesions around the penis, breasts, and axillary folds. Itching can be extreme. Because *Sarcoptes scabiei* is quite small, all that can be seen with the naked eye are the burrows and excoriations

around small pruritic vesicles. Scabies often spares the head. Immunocompromised patients, such as those with HIV, are particularly vulnerable to an extremely exuberant form of scabies with severe crusting and malodorousness, known as Norwegian scabies.

Diagnosis in all cases is confirmed by scraping out the organism after mineral oil is applied to a burrow; however, skin scrapings are usually not necessary and are not routinely done.

Treat with permethrin. Lindane (Kwell) has equal efficacy, but also greater toxicity. Lindane should not be used in pregnant women. Ivermectin is a suitable alternative and is given as oral therapy if the disease is extensive. Treat Norwegian scabies with a combination of permethrin and ivermectin.

Pediculosis

Pediculosis is skin infestation by lice. It is caused by the following:

- Head: *Pediculus humanus capitis*
- Body: *Pediculus humanus corporis*
- Pubic area: *Phthirus pubis* ("crab louse")

Patients present with itching, excoriations, erythematous macules and papules, and sometimes secondary bacterial infection. Diagnosis is made by direct examination of the pubic area, axillae, scalp, and other hair-bearing surfaces for the organism (louse or nits). Treat with permethrin or lindane (Kwell).

TOXIN-MEDIATED DISEASES

Toxic Shock Syndrome

Toxic shock syndrome (TSS) is a systemic reaction to a toxin produced from *Staphylococcus* attached to a foreign body. The majority of cases now are not from a menstrual source, such as a tampon or vaginal packing. Nasal packing, retained sutures, or any other form of surgical material retained in the body can promote the growth of the type of staphylococci that produces the toxin.

Because there is no single specific test, cases are matters of definition.

TSS is defined as the presence of 3 or more of the following findings:

- Fever >102 F
- Systolic BP <90 mm Hg
- Desquamative rash
- Vomiting
- Involvement of the mucous membranes of the eyes, mouth, or genitals
- Elevated bilirubin
- Platelets <100,000

In addition, TSS is a systemic disease:

- Raises creatinine, creatine phosphokinase, and liver function tests
- Lowers platelet count
- Can cause CNS dysfunction such as confusion
- Often produces hypocalcemia (usually because of a diffuse capillary leak syndrome that drops the albumin level)

Streptococcal toxic shock syndrome is essentially the same.

To treat, remove the source of the infection and give vigorous fluid resuscitation, pressors (e.g., dopamine), and antibiotics. Empiric treatment is with clindamycin plus vancomycin until cultures return. In confirmed cases of methicillin-sensitive strains, treat with clindamycin plus an antistaphylococcal medication (oxacillin, nafcillin). In methicillin-resistant strains (MRSA), use vancomycin or linezolid.

Staphylococcal Scalded Skin Syndrome

Staphylococcal scalded skin syndrome (SSSS) is transmitted through physical contact with surroundings. It most commonly occurs in infants, young children, and the immunocompromised.

SSSS is mediated by a toxin from *Staphylococcus*. The major presentation is the loss of the superficial layers of the epidermis in sheets. Nikolsky sign is present. It is markedly different from toxic shock syndrome in that there is normal BP and no involvement of the liver, kidney, bone marrow, or CNS.

Patients should be managed in a burn unit and given oxacillin or other antistaphylococcal antibiotics. Consider vancomycin because of possible MRSA.

Note

Differential Diagnosis

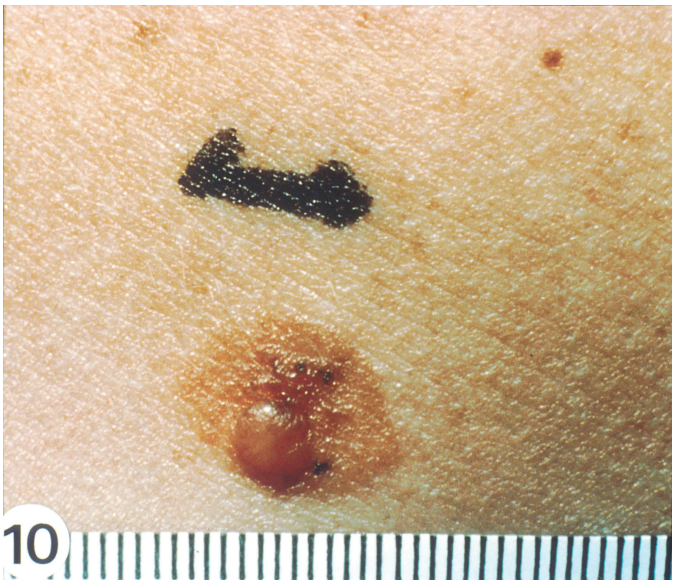
SSSS: from an infection; splits off only the superficial granular layer of skin

TEN: from drug toxicity; splits off the full-thickness of skin

BENIGN AND PRECANCEROUS LESIONS

The predominant method of distinguishing between benign and malignant lesions is by the shape and color of the lesion.

Benign lesions, such as the junctional or intradermal nevus, do not grow in size and have smooth, regular borders with a diameter usually <1 cm. In addition, they are homogenous in color, and this remains constant. Biopsy is the most accurate method of making a diagnosis, and benign lesions need to be removed only for cosmetic purposes.



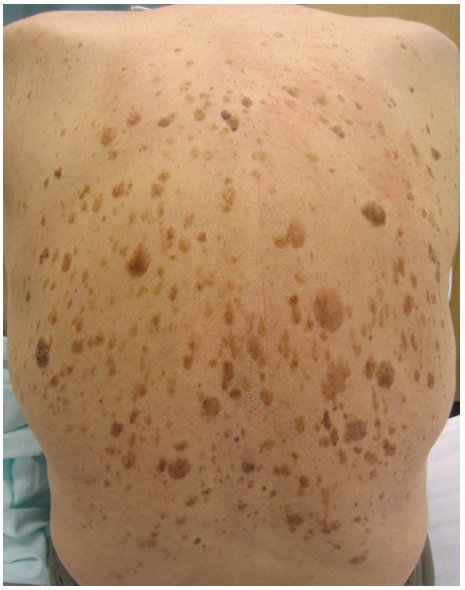
visualsonline.cancer.gov

Figure 12-5. Dysplastic Nevus

Seborrheic Keratosis

Seborrheic keratosis is a benign condition with hyperpigmented lesions occurring in the elderly. It has no malignant potential and no relation to either actinic keratosis or seborrheic dermatitis. Lesions have a "stuck on" appearance and are most common on the face, shoulders, chest, and back.

Lesions are removed only for cosmetic purposes with liquid nitrogen or curettage.



Wikipedia, James Heilman, MD

Figure 12-6. Seborrheic Keratosis

Actinic Keratosis

Actinic keratosis presents with precancerous lesions occurring on sun-exposed areas of the body in older persons. Lesions occur more often in those with light skin color. They contain chromosomal abnormalities, and although only 1:1,000 lesions progresses to squamous cell cancer, an individual patient may have dozens of them. Hence, the rate of transformation to squamous cell cancer is 0.25% per patient.

Although the lesions are usually asymptomatic, they can be tender to the touch and lighter in color.

Lesions should be removed with cryotherapy, topical 5 fluorouracil (5-FU), imiquimod, topical retinoic-acid derivatives, or even curettage. Advise patients to use sunscreen to prevent progression and recurrence.

MALIGNANT DISEASES

Melanoma

Superficial spreading melanoma is the most common type of malignancy, accounting for 70% of cases. The rate of occurrence of melanoma is rising faster than any other cancer in the United States.

Malignant lesions grow in size, have irregular borders, are uneven in shape, and have inconsistent coloring. Lentigo maligna melanoma arises on sun-exposed body parts in the elderly. Acral-lentiginous melanoma arises on the palms, soles of feet, and nail beds.

Biopsy diagnosis is best performed with a full-thickness sample because tumor thickness is by far the most important prognostic factor.

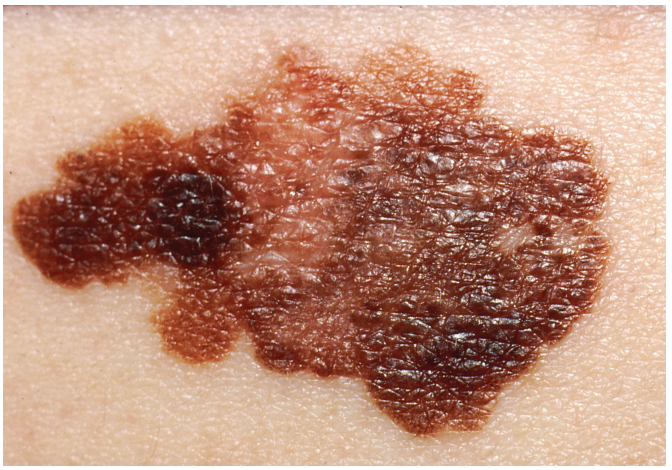
Table 12-1. Ten-Year Survival Rates for Melanoma

Lesion Size (mm)	Survival Rate
<0.76	96%
0.76–1.69	81%
1.7–3.6	57%
>3.6	31%

Melanoma is removed by excision. Huge 5-cm margins are not routinely indicated. The size of the margin is determined by tumor thickness.

- Melanoma in situ needs only 0.5-cm margin
- Lesions <1 mm in thickness get 1.0-cm margin
- Lesions 1- to 2-mm in depth get 2-cm margin
- Lesions >2 mm in depth get 2- to 3-cm margin

There is no definitive chemotherapy for any form of skin cancer. Interferon seems to reduce recurrence rates.



National Cancer Institute

Figure 12-7. Melanoma

Squamous Cell Carcinoma

Squamous cell carcinoma makes up 10–25% percent of all skin cancers. It develops on sun-exposed skin surfaces in elderly patients. It is particularly common on the lip, where the carcinogenic potential of tobacco is multiplicative.

Ulceration of the lesion is common. Metastases are rare (3–7%).

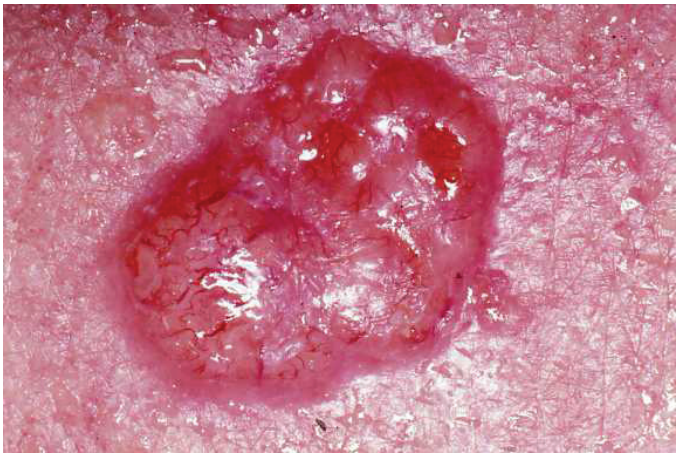
Diagnosis is confirmed with biopsy. Treatment is surgical removal. Radiotherapy can be used for lesions that cannot be treated surgically.

Basal Cell Carcinoma

Basal cell carcinoma makes up 65–80% of all skin cancers. It has a shiny or "pearly" appearance. Metastases are very rare (<0.1%).

Diagnosis is confirmed with shave or punch biopsy. Treatment is surgical removal. Mohs microsurgery has the greatest cure rate: instant frozen sections are done to determine when enough tissue has been removed to give a clean margin.

5-FU can be used in the treatment of superficial lesions.



Wikimedia, John Hendrix

Figure 12-8. Basal Cell Carcinoma

Kaposi Sarcoma

The causative organism of Kaposi sarcoma is Human herpes virus 8. These are purplish lesions found on the skin, predominantly of patients with HIV and CD4 <100/mm^3.

Treatment is antiretroviral therapy to raise CD4 count. When that does not occur, the specific chemotherapy for Kaposi sarcoma is liposomal doxorubicin hydrochloride or vinblastine.

Clinical Recall

What is the margin of excision of a suspected melanoma that has an in-depth thickness of 1.5 mm?

A. 0.5 cm margin

B. 2 cm margin

C. 3 cm margin

D. 4 cm margin

Answer: B

SCALING DISORDERS (ECZEMA)/PAPULOSQUAMOUS DERMATITIS

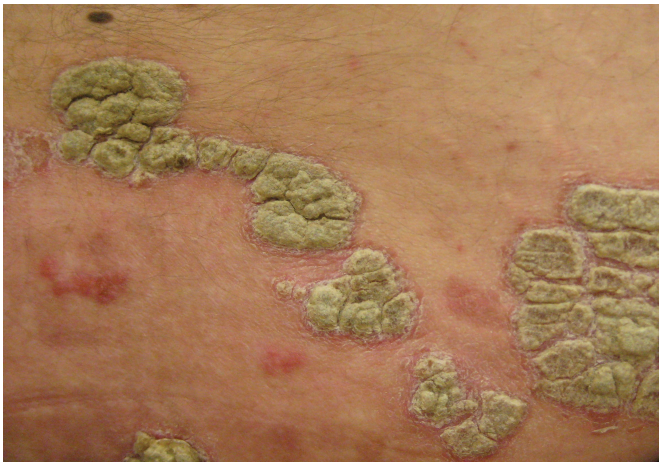
Psoriasis

The etiology of psoriasis is unknown. Silvery scales develop on the extensor surfaces, either locally or extensively. Nail pitting is a common accompaniment. The Koebner phenomenon is the development of lesions with epidermal injury.

Treatment. Salicylic acid is used to remove heaped-up collections of scaly material so that the other therapies can make contact. If the disease is relatively localized, topical steroids are used. Severe disease also needs coal tar or anthralin derivatives. To avoid the long-term use of steroids, which can cause skin atrophy, and to avoid coal tars, which are messy to use, substitute topical vitamin D and vitamin A derivatives. The vitamin D derivative most frequently used is calcipotriene. Tazarotene is a topical vitamin A derivative.

All patients should use emollients such as Eucerin™, Lubriderm™, or mineral oil. When >30% of the body surface area is involved, it is difficult to routinely use topical therapy to control disease. Ultraviolet light in that case is the most rapid way to control extensive disease. The most severe, widespread, and progressive forms of the disease can be controlled with methotrexate; however, it has the highest toxicity and may cause liver fibrosis.

The newest therapy is immunomodulatory biologic agents, such as alefacept, efalizumab, etanercept, and infliximab. These are monoclonal antibodies that target defects in the immune system, such as tumor necrosis factor.



Wikipedia, James Heilman, MD

Figure 12-9. Psoriasis

Atopic Dermatitis

Atopic dermatitis is an extraordinarily pruritic disorder characterized by high IgE levels. Red, itchy plaques appear on the flexor surfaces. In children, lesions are common on the cheeks and scalp. Adults present with lichenification.

Active disease is managed with topical steroids, antihistamines, coal tars, and phototherapy.

- Use antistaphylococcal antibiotics if there is impetiginization of the skin
- Use topical immunosuppressants such as tacrolimus and pimecrolimus to decrease dependence on steroid use
- Every effort must be made to avoid scratching; the topical tricyclic doxepin can be used to help stop pruritus

Preventive therapy is achieved by keeping the skin moist with emollients, avoiding hot water and drying soaps, and using only cotton clothes, as patients with this condition are extremely sensitive to drying.

Seborrheic Dermatitis

An oversecretion of sebaceous material and a hypersensitivity reaction to a superficial fungal organism, *Pityrosporum ovale*, underlie seborrheic dermatitis. Patients present with "dandruff," which may also occur on the face. Scaly, greasy, flaky skin is found on a red base on the scalp, eyebrows, and in the nasolabial fold.

Treatment is low-potency topical steroids such as hydrocortisone, or topical antifungals in the form of shampoo such as ketoconazole or sulfide. Zinc pyrithione is also used as a shampoo.

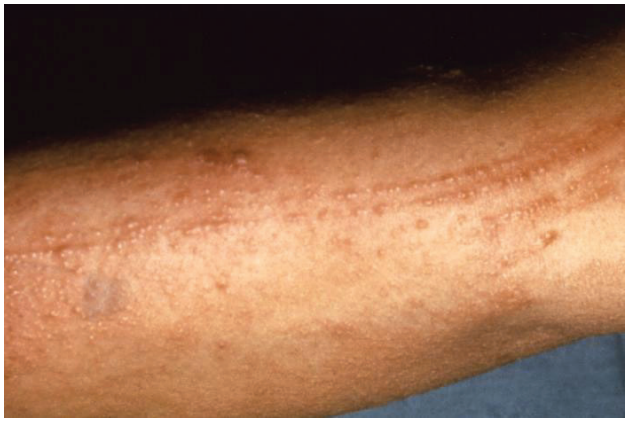
Stasis Dermatitis

Stasis dermatitis is a hyperpigmentation built up from hemosiderin in the tissue. It occurs over a long period, from venous incompetence of the lower extremities leading to the microscopic extravasation of blood in the dermis. There is no way to reverse this problem. Prevention of progression is with elevation of the legs and lower-extremity support hose.

Contact Dermatitis

Contact dermatitis is a hypersensitivity reaction to soaps, detergents, latex, sunscreens, or neomycin over the area of contact. Jewelry is a frequent cause, as is contact with the metal nickel from belt buckles and wristwatches. It can occur as linear, streaked vesicles, particularly when it is from poison ivy.

A definitive diagnosis can be determined with patch testing. Once the causative agent has been identified, treat with antihistamines and topical steroids.



phil.cdc.gov

Figure 12-10. Contact Dermatitis Due to Poison Ivy

Pityriasis Rosea

Pityriasis rosea is a pruritic eruption that often begins with a "herald patch," a single, pink, oval scaly patch before a full eruption of widespread rash is seen.

It is erythematous, salmon-colored, and looks like secondary syphilis, except that it spares the palms and soles. The lesions on the back appear in a pattern like a Christmas tree.

This condition is mild, self-limited, and usually resolves in 8 weeks without scarring.

This is a clinical diagnosis. VDRL/RPR is negative. Treat very itchy lesions with topical steroids.

DECUBITUS (PRESSURE) ULCERS

Decubitus ulcers are chronic sores that occur in the pressure areas of the body, where bone is closer to the skin. They are often associated with patients who are immobilized or bedridden.

Clinical presentation is in stages.

- Stage I lesions consist of **nonblanchable redness**.
- Stage II lesions result in **destruction of the superficial epidermis or partial destruction of the dermis**.
- Stage III lesions have **destroyed the full thickness of the skin but not the fascia**.
- Stage IV lesions show **destruction all the way to the bone**.

Diagnosis. Never culture a swab of the superficial ulcer or drainage from the ulcer. It will be impossible to determine whether it is a genuine infection or simply colonization. A definitive microbiologic diagnosis is often obtained only in the operating room after debridement.

The major theme of treatment is to relieve pressure. If the lesions are definitely infected, then antibiotics are useful.

HAIR

Alopecia Areata

Alopecia areata is an autoimmune disease in which antibodies attack the hair follicles and destroy hair production. Most cases will resolve spontaneously over time. Immediate treatment is localized steroid injection into the area of hair loss.

Telogen Effluvium

Telogen effluvium is the loss of hair in response to an overwhelming physiologic stress, such as cancer or malnutrition. Treatment is correction of the underlying stress or disease.

ACNE

The contributing organism for acne is *Propionibacterium acnes*. Pustules and cysts occur, which rupture and release free fatty acids, which in turn causes further irritation. Acne is more common in girls, but boys have more severe disease.

Patients present both with closed comedones (which are white) and open comedones (which are black). The discharge, although purulent, is odorless.

Treat mild disease with a topical antibiotic (clindamycin, erythromycin, sulfacetamide) plus the possible addition of the bacteriostatic agent benzoyl peroxide. If the attempts to control the load of bacteria locally are ineffective, use topical retinoids.

Treat moderate disease with benzoyl peroxide plus a retinoid (tazarotene, tretinoin, adapalene).

Treat severe cystic acne with an oral antibiotic (minocycline, tetracycline, clindamycin, oral isotretinoin). Oral retinoic-acid derivatives are a strong teratogen.

Clinical Recall

Which of the following treatment strategies is used to control extensive psoriasis (>30% BSA)?

A. Topical emollients

B. Topical vitamin A

C. Topical vitamin D

D. Phototherapy

E. Topical steroids

Answer: D

Radiology/Imaging 13

Learning Objectives

- ❑ List the indications and common abnormal findings for chest x-ray, abdominal x-ray, PET scan, bone scan
- ❑ Answer questions about different approaches to visualizing the CNS

This concise section should help you understand the types of tests offered in radiology.

CHEST X-RAY

The most basic radiologic examination is a chest x-ray. Standard x-rays are based on the degree of density of tissue and how much x-ray energy each type of tissue will absorb.

- The closer a bone structure is in density, the greater the energy it will absorb.
- Therefore, because bones block the most amount of x-ray energy, they will come out white on the film.
- Conversely, air absorbs or blocks the least amount of energy and thus will appear darkest.

Chest x-rays are **not routine** screening tests. There is no routine screening of the general population for cancer or tuberculosis. You can do a chest x-ray if the PPD skin test is positive, but that is not the same thing as just doing a general screening.

Most x-rays are **posterior-anterior (PA)** films. The x-ray plate is placed in front of the chest, and the patient leans forward against the plate. The x-ray beam is directed from posterior to anterior. The patient must be able to stand for a PA film to be performed.

Anterior-posterior (AP) films are less accurate but must be done if the patient is too ill or unstable to stand up.

- All patients with central venous lines or chest tubes
- Unstable patients, such as those in intensive care

The single greatest difference between the film types is heart size:

- AP films will show a heart size that is artificially enlarged; that is because the heart is more anterior in the chest and will therefore cast a wider shadow.
- **AP films** will show a heart >50% of the total transthoracic diameter, while normal **PA films** will show a heart <50%.

Note

The phenomenon produced by **AP film** is no different than holding your hand in a light shined against a wall. The farther your hand is away from the wall, the larger your hand's shadow will appear.

Technical Aspects of Normal Film Quality

- When examining a chest x-ray, first assess the film for its technical quality. If the patient's body is abnormally rotated, the film will be less accurate. You can determine this by seeing if the trachea and the spinous apophysis are midway between the clavicles.
- Perform chest x-ray when the patient is holding in a full inhalation. There should be at least 10 ribs visible, counting from top to bottom.
- An underexposed film will have the structures appearing too white, while an overexposed film will have the blood vessels appearing too dark (preventing one from accurately assessing the blood vessels).
- Note that on a PA film, the right hemidiaphragm is typically higher than the left. That is because the liver is underneath the right hemidiaphragm, pushing it up.

Expiratory Film

Expiratory film is used when one is looking for a pneumothorax. The lungs will appear smaller because less air will remain in the lungs on expiration. Because a pneumothorax is air outside the lungs in the pleural space, this air will appear relatively larger. The volume of air in the pleural space does not decrease on exhalation.

Lateral Chest X-ray

Lateral chest x-ray will determine whether a structure in the chest is more anterior or posterior. For example, it can determine whether a mass that is visible in the center of the mediastinum on a PA film is posterior, making it more likely to be a neurally derived tumor attached to the spinal cord or an anterior mass. Anterior mediastinal masses are from the thymus, thyroid, lymph nodes, or a teratoma.

Note

The right hemidiaphragm will appear higher on a lateral x-ray and a PA film because the liver pushes it upward.

Lateral x-ray also has a greater sensitivity for the detection of small pleural effusions.

- On a PA film, at least 100-200 mL of fluid need to be present to even begin to see an effusion. Each hemithorax can contain 3 liters of fluid if it is filled to capacity.
- Lateral chest x-ray can detect as little as 50 mL.
- These figures represent the amount of fluid needed to barely begin seeing "blunting," or obliteration, of the costophrenic angle.

On a lateral x-ray, the right hemidiaphragm is the one crossing the heart shadow.

Decubitus Film

Decubitus film helps detect the presence of a pleural effusion. It is taken with the patient lying on his side, and is employed when blunting or obscuration of the costophrenic angle is seen on a PA or lateral x-ray.

Effusions will move and form a layer on the side of the chest wall. Infiltrates from alveolar disease do not move with gravity. You cannot determine if an effusion is infected just from its appearance on an x-ray.

Common Disorders Seen on Chest X-ray

COPD/Emphysema

The most common appearance of COPD on a chest x-ray is related to **hyperinflation of the lung**. This leads to an increased anterior/posterior diameter ("barrel chest").

- Leads to a darkening of the lung fields because more air is present
- Trapped air flattens the diaphragm and gives the impression of an elongated or tubular-shaped heart because it has been stretched down
- Bullae may be seen (large, air-filled cavities that can give thin, white lines on a chest x-ray as walls of the cavities press up against each other)

Pneumonia

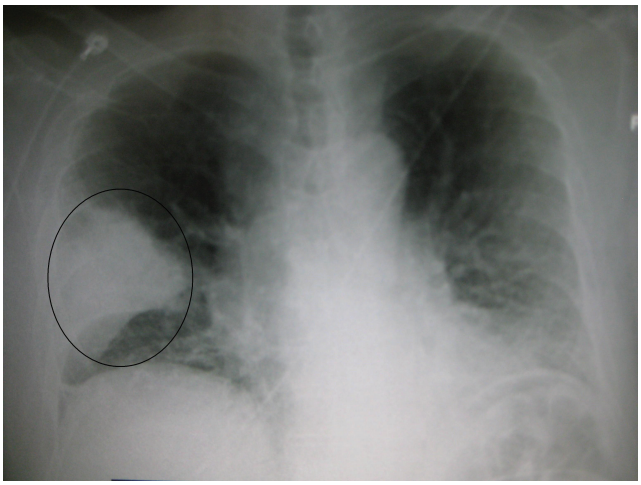
Lobar pneumonia causes a whitening of each individual lobe of the lung because of greater density of the lung.

- "Silhouette" sign is present (border between the affected lobe and surrounding denser structure is obscured).
- Density of the lung increases because of alveolar infiltration to the point where it takes on the density of the nearby heart or diaphragm; thus, one can no longer tell where the lung ends and the nearby denser structure begins.
- **Lower lobe** pneumonia gives a silhouette over each half of the diaphragm. **Right middle-lobe** pneumonia obscures the right heart border and will not pass the minor or horizontal fissure seen on a PA chest x-ray. **Upper-lobe** infiltration will not pass the major fissure, and this is more easily seen on a lateral x-ray. You cannot determine a specific microbiologic etiology from the x-ray alone.
- Diseases of the lung outside the airspace but in the interstitial membrane give a fine, lacy appearance visible in most, if not all, of the lobes. Disorders which give interstitial infiltrates include *Pneumocystis* pneumonia, *Mycoplasma*, viruses, chlamydia, and sometimes *Legionella*. Noninfectious etiologies of an interstitial infiltrate are pulmonary fibrosis secondary to silicosis, asbestosis, mercury poisoning, berylliosis, byssinosis (from cotton), or simply idiopathic pulmonary fibrosis. As the long-standing disorders become worse and more chronic, a greater degree of fibrosis occurs and leads to greater thickening of the membrane (described as *reticular-nodular* and, later, *honeycombing).*

Note

Interstitial Syndromes of the Lung include:

Sarcoidosis
Histiocytosis X
IPF (interstitial pulmonary fibrosis)
Tumor
Failure
Asbestosis
Collagen disorders
Environmental
Dust
Drugs



Wikipedia, James Heilman, MD

Figure 13-1. Pneumonia

Congestive Heart Failure

The majority of pulmonary vascular flow is normally at the base of the lungs because of gravity. When there is fluid overload, the blood vessels toward the apices become fuller (called pulmonary vascular congestion or "cephalization" of flow). The term *cephalization* is used because more flow is moving toward the head.

The other findings associated with CHF are cardiomegaly, effusions, and Kerley B lines.

Note

The subtle radiologic finding with a Kerley B line is less important today in the evaluation of congestive heart failure, since the advent of echocardiography.

Kerley B lines are the least important. They are small, horizontal lines at the bases that represent fluid in the interlobular septa. Each lung has several lobes. When fluid builds up outside the lobes, this is known as a pleural effusion. When fluid builds up within each lobe, in between the lobules, this is known as a Kerley B line.

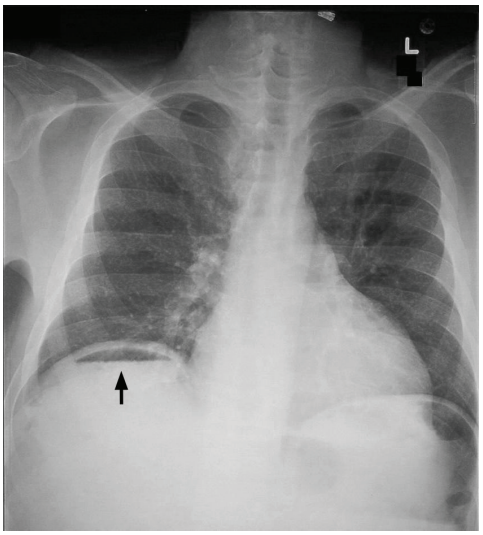
Position of Lines and Tubes

Chest x-ray is routinely used to determine the appropriate position of central venous lines and both endotracheal and chest tubes. The proper position of the tip of an endotracheal tube is 1 to 2 cm above the carina.

- Keep some space above the carina to make sure the tube doesn't push into it when the head moves forward. That would be extremely uncomfortable and will provoke coughing.
- The tip of central venous lines is at the junction of the superior vena cava and the right atrium, at the point where the right mainstem bronchus is seen.
- The tip of the line should not be fully inside the atrium because this can irritate the heart and may provoke an arrhythmia.

Air under the Diaphragm

When there is perforation of an abdominal hollow organ, such as the duodenum, air is released and is visible under the diaphragm. The proper film to detect this is a chest x-ray taken in the upright position. This will allow the air to collect under the diaphragm, which should be easily visible. Abdominal x-rays do not always visualize the top of the diaphragm because of differences in body size. Chest x-rays always visualize the top of the diaphragm.



Wikimedia, Clinical Cases

Figure 13-2. Pneumoperitoneum

Imaging Tools for Lung Parenchyma

High resolution CT scan provides greater detail than a chest x-ray or CT scan because of 1 mm cut. This has a sensitivity of 95% and a specificity of close to 100% for lung parenchymal disease. High resolution CT scan is indicated in the following conditions:

- Symptomatic patients with a normal chest x-ray
- Detecting metastatic lesions, solitary nodules, bullae, bronchiectasis, and diffuse parenchymal disease (i.e., idiopathic lung diseases)
- To determine the type of lung biopsy required and site of biopsy

Clinical Recall

Which of the following is an indication for getting an expiratory chest x-ray?

A. Pleural effusion

B. Tuberculosis

C. COPD

D. Pneumothorax

E. Congestive heart failure

Answer: D

ABDOMINAL X-RAY

Compared with chest x-rays, standard abdominal films without barium contrast provide far less information.

- Beneficial only in the detection of an abdominal obstruction, such as an ileus or a volvulus
- **Do not** reliably detect mass lesions, polyps, cancer, ascites, IBD

Use the following guidelines for detection:

- Mass lesions in all abdominal organs are best detected with CT scan or MRI of the abdomen.
- Polyps are best detected by colonoscopy.
- Ascites are visualized by U/S or CT scan.
- IBD, diverticulosis, and cancer are best detected by endoscopy or barium study of the bowel.
- Although 80–90% of kidney stones (nephrolithiasis) can be seen on abdominal films, they are also best detected by U/S or CT scan. Only 10–15% of gallstones can be detected on an abdominal film because most of them do not calcify.
- Pancreatic calcifications can be detected in 30–50% of patients with chronic pancreatitis.

Sonography (U/S)

Sonography is used for evaluation of abdominal and pelvic pathology. Sonograms should be employed first for evaluation of the biliary tract because of their accuracy in evaluating dilation and obstruction of the ducts. The majority of cholelithiasis should be detected with sonography because cholesterol gallstones should be easily visible by sonography. The majority of nephrolithiasis is visible by sonography, although there is less accuracy in detecting stones in the ureters because they become retroperitoneal structures.

Sonography is useful in the evaluation of masses in the liver, spleen, pancreas, and pelvis, as well as for evaluating the presence of ascites. Despite this accuracy, CT scanning tends to have a greater sensitivity and specificity for the abdomen and pelvis. Sonography is particularly valuable in the evaluation of pregnant patients because it avoids radiation exposure to the fetus. Although less accurate, sonography is also practical in patients who have an absolute contraindication to the use of IV contrast. A total of 1:10,000 patients have a life-threatening reaction to the use of iodinated contrast agents.

There is very little utility of sonography in the evaluation of thoracic structures because the ribs block the sound waves. Also, sonography in the evaluation of intracranial structures, such as the brain, is not recommended because the skull blocks the sound waves.

Endoscopic U/S involves introducing a sonographic device into the abdomen at the end of an endoscope. Endoscopic U/S is extremely accurate in evaluating pancreatic pathology that is not easily visualized on CT scanning, such as a gastrinoma. Pancreatic lesions can also be effectively evaluated in this way.

Endoscopic Retrograde Cholangiopancreatography

Endoscopic retrograde cholangiopancreatography (ERCP) is an endoscopically introduced contrast procedure designed to visualize the biliary tract and pancreatic structures. ERCP is for therapy. The endoscope is introduced into the small bowel, and a catheter is placed through the sphincter of Oddi. Contrast is injected through the catheter. This allows extremely accurate visualization of the pancreatic ductal and biliary systems. ERCP is excellent for detecting strictures, stones, and neoplastic causes of obstruction. The other advantages of ERCP are the ability to perform therapy with the removal of these stones, to dilate strictures, and to perform biopsies. The scope does not routinely go up the sphincter of Oddi because it is too large to pass.

MRCP is an MRI alternative to ERCP. It is less invasive than ERCP but does not allow an intervention.

The most common complication of ERCP is acute pancreatitis (around 10% in some series). Most of the time the pancreatitis is mild.

Barium Studies

Barium studies of the large bowel are never as accurate for colonic pathology as is endoscopy. In addition, you cannot biopsy with barium studies or perform therapeutic procedures, such as cautery or epinephrine injection for bleeding. The upper GI series is never as accurate as is upper endoscopy for the same reasons.

However, barium studies of the esophagus are a good test to start with for the evaluation of esophageal pathology. Barium esophagogram is particularly good for the detection of strictures, rings, and webs, or Zenker diverticulum. Barium is not as accurate as an upper endoscopy for the detection of esophageal cancer because a biopsy is required. (Endoscopy is far superior for the detection and therapy of esophageal varices as well.) Barium is not as accurate as manometry for the confirmation of the diagnoses of achalasia or muscular disorders, such as diffuse esophageal spasm and nutcracker esophagus.

Note

MRCP: diagnosis

ERCP: treatment

Clinical Pearl

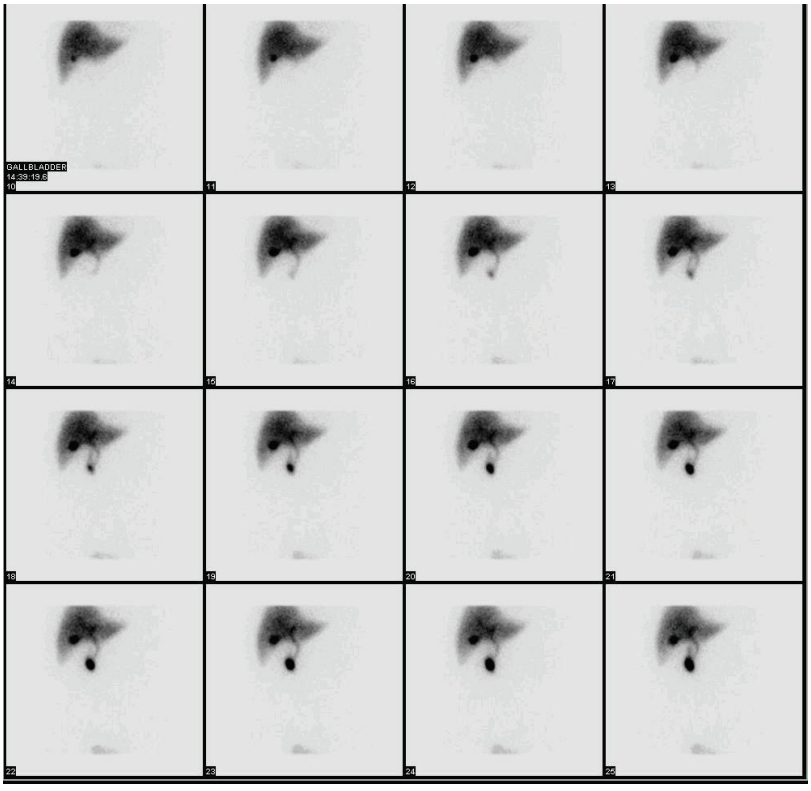
Capsule endoscopy is not a screening test to detect colon cancer. Perform capsule endoscopy to evaluate obscure small bowel GI bleeding.

Capsule Endoscopy

The ileum and jejunum are the hardest parts of the bowel to visualize by radiologic studies or endoscopy. In the past, a "push enteroscopy" was performed by introducing an extremely long, thin scope into the small bowel. Capsule endoscopy is a new technology that allows direct visualization of the small bowel by swallowing a camera that electronically relays thousands of photographic images from the small bowel to a receiver outside the body. The drawback of this procedure is that it is not possible to perform therapeutic interventions in this way. If a patient has GI bleeding that is serious and both upper and lower endoscopy do not reveal the source, then answer "capsule endoscopy" on the exam.

HIDA Scanning

This is a nuclear medicine scan useful only in the detection of acute cholecystitis. HIDA scanning is most useful in patients in whom the diagnosis of cholecystitis is not clear. An abnormal or positive test is the lack of visualization of the gallbladder. This is because the neck of the gallbladder or cystic duct becomes too edematous to allow the passage of the nuclear material. A normal scan will visualize the gallbladder. An abnormal scan will not visualize or fill the gallbladder.



Wikimedia, Myo Han

Figure 13-3. HIDA Scan

Virtual Colonoscopy

This procedure uses CT scan or MRI to provide a computer-simulated bidimensional or tridimensional image of the air-filled, distended colon.

PET SCAN

Positron emission tomography (PET) scans are useful in the detection of cancer. They are particularly useful in determining whether lesions that are visible on a CT scan of the chest are malignant or benign. Cancer is typically associated with the increased uptake of fluorodeoxyglucose. PET scanning is used after chemotherapy to assess for the presence of residual cancer in some patients and can also be used to determine whether a patient is an operative candidate to remove a primary cancer. If the PET scan does not reveal malignancy, then the resection of certain primary cancers, such as lung cancer, is more likely to be successful.

Remember that slow-growing cancers (e.g., bronchoalveolar) may have a negative PET scan. Be careful when evaluating pulmonary nodules with PET scanning.

Clinical Pearl

Always check the patient's glucose before doing a PET scan. If the glucose is elevated, the PET scan can be falsely negative.

CENTRAL NERVOUS SYSTEM VISUALIZATION

In general, the most accurate test for evaluating the CNS is the MRI. The MRI is superior for the detection of stroke, cancer, MS, and infections and in the evaluation of the posterior fossa, such as the cerebellum and brainstem.

The CT scan does not visualize the brainstem well. For example, a stroke is visible on an MRI in >90% of cases within the first 24 hours after its onset, whereas the CT scan needs 3 to 4 days before >90% are visible. This is because the MRI is based on the water content of tissues rather than on the calcium content or simple density of tissue. Within a few hours after the onset of a stroke, the cells begin to swell and increase their water content. This is immediately visible on an MRI, whereas for a CT scan to detect an abnormality, the cells must die to decrease the density of visible cells.

The single exception in which a CT scan is superior to an MRI is in the detection of blood. As soon as bleeding occurs, it is visible on a CT scan. Therefore, the two cases in which a CT scan is a better study are to evaluate head trauma and to exclude hemorrhagic stroke. When a patient arrives within 3 hours of the onset of the symptoms of a stroke, a CT scan is first performed to exclude hemorrhage. This is to see if a patient is eligible for the use of thrombolytic therapy within these first 3 hours.

CT scan is also used first for the detection of subarachnoid hemorrhage. On the first day after the stroke's onset, the CT scan has 95% sensitivity. The sensitivity diminishes by about 5% per day as the blood is hemolyzed and removed.

Contrast on a scan of the head is indicated primarily for the detection of cancers and infection. When an abscess or neoplastic process is present, there is some disruption of the blood-brain barrier, causing some extravasation of the contrast, which is visible as a contrast, or "ring"-enhancing lesion around the mass.

BONE IMAGING

An x-ray is certainly the first study to implement when evaluating trauma and fracture. Unfortunately, the bone scan has much less specificity and does not reliably distinguish between bone infection and infection of the overlying soft tissue. The MRI is 90–95% sensitive and 90–95% specific.

Osteomyelitis

When there is the suspicion of osteomyelitis, an x-ray is done first. Although plain x-rays lack sensitivity for the first 1 to 2 weeks, the specificity for osteomyelitis is excellent. More than 50% of the calcium content of bone must be lost for osteomyelitis to be visible. The earliest finding of osteomyelitis on an x-ray is elevation of the periosteum. If the film returns normal and there is still suspicion of osteomyelitis, then the best test is an MRI. The MRI and technetium nuclear bone scan have the same sensitivity (90–95%); however, the MRI's specificity is far greater (90–95%). Both studies should become abnormal within 2 days of the onset of osteomyelitis. Therefore, a negative bone scan is very useful if it is normal; it means that there is no osteomyelitis. If it is abnormal, you may still need to perform an MRI.

Clinical Recall

Which of the following findings on chest x-ray will be seen with a perforated peptic ulcer?

A. Kerley B lines with vascular cephalization

B. Blunting of the costophrenic angles with a clear meniscus sign

C. Pneumoperitoneum

D. Flattening of the diaphragm with a tubular shaped heart

E. Interstitial hyperdensities with hilar lymphadenopathy

Answer: C

Ophthalmology 14

Learning Objective

- ❑ Describe the presentation and treatment of glaucoma, cataracts, keratitis, uveitis, periorbital cellulitis, retinal diseases, and conjunctival diseases

RETINAL DISEASES

Diabetic Retinopathy

The etiology of diabetic retinopathy is based on damage to the endothelial lining of the small blood vessels of the eye. The endothelial lining of the retinal vessels becomes damaged, leading to progressive occlusion on a microscopic level. The occlusion leads to obstruction and increased pressure.

- The earliest form of this adverse effect on the retina is called **nonproliferative** (or **background**) retinopathy. It is characterized by dilation of veins, microaneurysms, retinal edema, and retinal hemorrhages. Hemorrhages into the retina are not as damaging as intravitreal hemorrhages because they do not obstruct sight.
- **Proliferative** retinopathy is a more advanced form of the disease and is markedly more serious, meaning it progresses more rapidly to blindness.
  - As the microvascular damage to the vessels worsens, the vessels secrete increased amounts of an angiogenesis factor (thus, "nutrition" to the retina decreases).
  - In an effort to deliver more nutrition and oxygen to the retina, the vessels exert an increased effort to have more of them produced.
  - This "neovascularization," or new blood vessel formation, leads to the optic nerve getting covered with abnormal new vessel formation. In addition, hemorrhages protrude into the vitreous chamber.

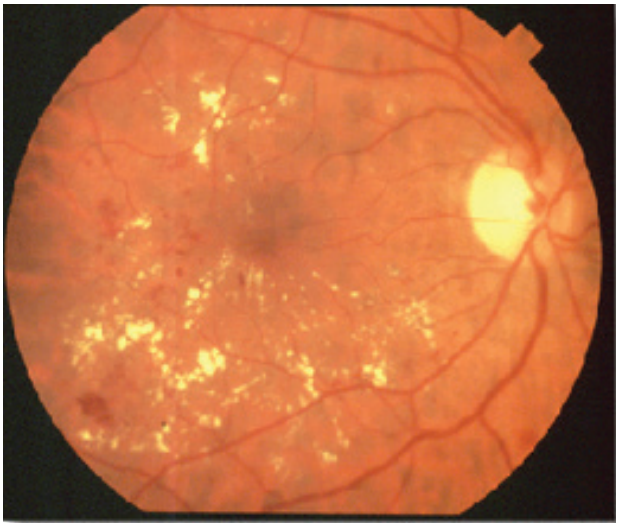
Clinical Correlate

The etiology of diabetic retinopathy is identical in pathogenesis to the damage that diabetes causes to all blood vessels in the body, such as in the heart, kidney, brain, and peripheral nervous system.

Note

Vitreal hemorrhage is much more serious than a microaneurysm or intraretinal hemorrhage because it is much more sight-threatening.

Symptoms are highly variable. There may be very advanced disease occurring with no symptoms. Vision may decrease slowly or rapidly. Vitreal hemorrhages may develop suddenly, and patients will complain of "floaters" in their vision.



Retina-Vitreous Surgeons of Central New York

Figure 14-1. Features of Diabetic Retinopathy

Diagnosis. Screening for the presence of retinopathy should be performed on an annual basis by an ophthalmologist. This is how candidates for fluorescein angiography and laser photocoagulation are found. Fluorescein helps identify which vessels should undergo laser photocoagulation. The laser selectively destroys focal areas of the retina and diminishes the production of the angiogenesis factor, which causes the proliferative retinopathy.

Treatment of both stages of diabetic retinopathy is tight control of glucose, BP, and lipid levels. For proliferative retinopathy, add immediate laser photocoagulation.

The more tightly the glucose is controlled within the normal range, the slower the progression of the retinopathy. Control BP to a level <130/80 mm Hg.

Aspirin, clopidogrel, and other platelet-inhibiting medications have shown no benefit.

Retinal Detachment

> A 71-year-old woman presents with blurry vision in her left eye since that morning. She says it was as if "a curtain came down." She has had floaters in the periphery of her left eye over the past few weeks but has had no pain or erythema. She has a history of stage I hypertension but is otherwise healthy.

Note

The term *rhegmatogenous*, which describes the detachment, is from the Greek word for "tear."

Retinal detachment is usually spontaneous, but it may result from trauma. The most common predisposing factors are myopia and surgical extraction of cataracts. Traction on the retina can also occur from proliferative retinopathy from diabetes, retinal vein occlusion, and age-related macular degeneration.

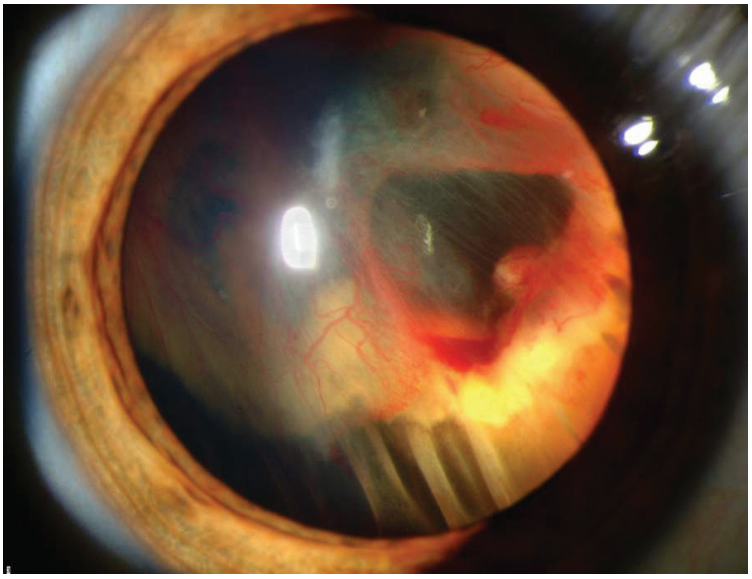
Symptoms include:

- Blurry vision in one eye without pain or redness (**most common**)
- Visualization of "floaters" in the eye, and flashes at the periphery of vision (sometimes described as a "curtain coming down," as the retina falls off the sclera behind it)

Diagnosis is made by ophthalmologic examination.

Treatment. Try to reattach the retina. Most uncomplicated rhegmatogenous retinal detachments can be cured with one operation, and a few require a second operation.

- Leaning the patient's head back, to promote the chance that the retina will fall back into place
- Surgical reattachment of the retina to the sclera, with laser photocoagulation, cryotherapy, or injection of expansile gas into the vitreal cavity (the gas will press the retina back into place)
- A "buckle," or belt placed around the sclera to push it forward so that it makes contact with the retina
- If no response to any method, consider removing the vitreous and surgically attach the retina to the sclera.



National Eye Institute/National Institutes of Health

Figure 14-2. Retinal Detachment

Age-Related Macular Degeneration

Age-related macular degeneration (ARMD) is the most common cause of legal blindness in older persons in the Western world. The etiology is unknown. ARMD is characterized by the formation of deposits of extracellular material collecting into yellowish deposits seen on ophthalmoscopy. These deposits are known as "drusen." They are small, granular, subretinal deposits that are age related.

There are 2 types of ARMD:

- **Dry**, or atrophic, form
  - Slowly progressive visual loss in the elderly
  - Leads to visual loss that is slow and gradual
  - Diagnosis is confirmed by finding clearly visible drusen on dilated eye exam
- **Wet**, or exudative, form
  - Abnormal growth of vessels from the choroidal circulation into the subretinal space
  - The vessels leak, leading to collections of subretinal fluid and a localized, exudative retinal detachment
  - Rapid distortion of vision over weeks to months
  - Diagnosis is confirmed with fluorescein angiography

Treatment.

- **Dry** form: nothing is proven to stop progression, but zinc, antioxidant vitamins C and E, and beta-carotene may slow progression
- **Wet** form: VEGF inhibitors ranibizumab and bevacizumab

Retinal Occlusions

Central Retinal Artery Occlusion

There are various etiologies of central retinal artery occlusion: carotid artery embolic disease, temporal arteritis, cardiac thrombi or myxoma, or any of the usual causes of thrombophilia such as factor V Leiden mutation.

Patients present with a sudden, painless, unilateral loss of vision. There is no redness of the eye. Ophthalmoscopy reveals a pale retina, with overall diminished perfusion and a "cherry-red" spot at the fovea. There is also "box-car" segmentation of the blood in the veins.

Diagnostic tests include carotid artery imaging, echocardiography, and evaluation for thrombophilia.

Treatment is similar to that of a stroke (cardiovascular accident or transient ischemia attack).

- Lay the patient flat
- Supply oxygen and ocular massage in an attempt to unobstruct the vessel
- Consider acetazolamide and thrombolytics
- Anterior chamber paracentesis may decompress the eye pressure and dislodge the embolus

Central Retinal Vein Occlusion

Patients with retinal vein occlusion are at particularly high risk for developing glaucoma. They should be monitored for the possible use of laser photocoagulation. Younger patients should be investigated for inherited causes of thrombophilia, such as factor V mutation, protein C deficiency, and antiphospholipid syndromes.

Presentation is similar to retinal artery occlusion: sudden loss of vision without pain, redness, or abnormality in pupillary dilation. Ocular examination by funduscopy reveals disk swelling, venous dilation, tortuosity, and retinal hemorrhages.

Retinal hemorrhage is the main way to distinguish **venous obstruction from arterial obstruction**. You can't have a hemorrhage in the retina if you don't have blood getting into the eye.

There is no specific treatment for retinal vein obstruction.

Clinical Recall

Which of the following fundoscopic findings is representative of proliferative diabetic retinopathy?

A. Dilation of veins, microaneurysms, retinal edema, and retinal hemorrhages

B. Vitreal hemorrhages with optic nerve concealment by neovascular growth

C. Floaters, red cells in the vitreous with a wrinkled, detached retina

D. Yellowish, small, and granular extracellular subretinal deposits

E. A pale retina with diminished perfusion and a cherry-red spot at the fovea

Answer: B

GLAUCOMA

Glaucoma is an irreversible eye disease associated with increased eye pressure and vision loss. The precise etiology is unknown.

Open-Angle Glaucoma

In open-angle glaucoma (**most common**, 90% of cases), there is a decrease in the outward flow/drainage of aqueous fluid from the anterior chamber, causing increased ocular pressure.

Patients are asymptomatic for a long time, explaining why it is important to screen older patients.

The first clue to the diagnosis is a **cup-to-disk ratio >0.5**, which should be confirmed by repeated elevation in intraocular pressure as determined by tonometry.

Treatment is to decrease the production of aqueous humor and increase its drainage.

- To **decrease the production of aqueous humor**: beta-blockers (timolol, betaxolol, levobunolol), alpha-adrenergic agonists (apraclonidine, brimonidine), and carbonic anhydrase inhibitors (dorzolamide and brinzolamide)
- To **increase the outflow of the humor**: prostaglandin analogs such as topical latanoprost, travoprost, and bimatoprost (side effects include causing the eyes to change color and darkening of the eyelids); pilocarpine (a miotic agent) constricts the pupil to allow greater outflow of the aqueous humor
- If no response to medical therapy, consider surgery, e.g., laser trabeculoplasty and surgical trabeculectomy.

Closed-Angle Glaucoma

Closed-angle glaucoma is often an ophthalmologic emergency precipitated by the use of medication with anticholinergic properties.

- Eye is red, painful, hard to palpation
- Associated with a fixed midpoint pupil
- Cornea has a hazy cloudiness
- Marked diminishment of visual acuity

Treatment is urgently needed.

- IV acetazolamide, urea, and osmotic diuretics such as mannitol and glycerol
- Pilocarpine to open the canal of Schlemm
- Beta-blockers to decrease humor production
- If no response, laser trabeculoplasty

CATARACTS

Cataracts are opacifications of the lens. They are slowly progressive, with a blurring of vision occurring over months to years. Glare from the headlights of cars is particularly a problem when driving at night. Color perception is reduced in general. The etiology of cataracts is unknown, although there is an association with cigarette smoking.

Mature cataracts can be easily seen on physical examination. Earlier-stage disease is seen with a slit lamp.

There is no medical therapy for cataracts. Surgical removal with the placement of an intraocular lens is the standard of care.

CONJUNCTIVAL DISEASES

Conjunctivitis

Conjunctivitis can occur from any infectious agent, including bacteria, viruses, and fungi. It is highly contagious.

- **Bacterial** conjunctivitis is often unilateral and presents with a marked purulent discharge from the eye.
  - Most symptomatic in the morning, when patient's eye has developed a significant crust overnight (can make it hard to open the eye)
  - Less itching with bacterial than with viral
  - Eye is red but there is a normally reactive pupil and normal ocular pressure
  - Visual acuity is not impaired
- **Viral** conjunctivitis is often bilateral, with enlarged preauricular adenopathy.
  - Severe ocular itching
  - Eyes are red but the pupils are normally reactive without photophobia (light sensitivity)

Treatment is as follows:

- **Bacterial** conjunctivitis: topical antibiotic such as erythromycin ointment, sulfacetamide drops, or topical fluoroquinolones
- **Viral** conjunctivitis: symptomatically with topical antihistamine/decongestants; there is no specific microbiologic treatment

Subconjunctival Hemorrhage

Subconjunctival hemorrhage is more dangerous in its appearance than in its actual damage to vision or even the eye itself. The most common cause is trauma, particularly in the presence of thrombocytopenia. The collection of the hematoma stops at the limbus, which is the anatomic connection between the conjunctiva and the cornea. Because this prevents the blood from covering the cornea, there is no impairment of vision.

There is no intraocular or intravitreal damage and hence no impairment of vision. No specific therapy is necessary.

Note

Subconjunctival hemorrhage looks more dangerous than it is.

KERATITIS

Keratitis refers to any infection or inflammation of the cornea. Usually, keratitis happens as a result of trauma to the cornea with the inoculation of bacterial or fungal elements into the cornea.

Herpes Simplex Keratitis

Herpes simplex keratitis is characterized by severe pain in the eye and a sensation that something is caught under the eyelid.

Diagnosis is based on finding a characteristic dendritic pattern over the cornea on fluorescein staining of the eye with examination under a blue light.

Treatment is oral acyclovir, famciclovir, or valacyclovir, plus topical trifluridine 1% solution or idoxuridine.

Note

Never use oral and topical steroids to relieve the inflammation of herpes simplex keratitis. That can markedly worsen the growth of the virus , acting as "fertilizer."

PERIORBITAL CELLULITIS

Cellulitis is caused by *Staphylococcus aureus* or *Streptococcus* invading the dermis and subcutaneous tissues surrounding the eye.

Treatment is an antistaphylococcal penicillin such as oxacillin or nafcillin. In cases of penicillin allergy, use a first-generation cephalosporin such as cefazolin.

UVEITIS

Uveitis occurs when the structures of the uveal tract (the iris, ciliary body, and choroid) become inflamed. It is caused by various systemic inflammatory conditions, such as psoriasis, sarcoidosis, syphilis, Reiter syndrome, and IBD.

Uveitis leads to a painful, red eye with marked photophobia. One clue to diagnosis is pain that occurs even when shining a light in the unaffected eye. This is because of the consensual light reflex in which the affected pupil will constrict even when light is shined in the normal eye.

Diagnosis is made by slit lamp examination. Inflammation of the iris, ciliary body, and choroid is visible. Inflammatory cells may accumulate on the inside of the cornea after they precipitate out of the aqueous humor, rather like an accumulating snowfall. These focal collections are called keratic precipitates.

Basic management, despite the varied underlying conditions, is to treat with topical or systemic steroids.

Clinical Recall

A 32-year-old man presents with redness of his eyes, marked photophobia, and normal conjunctiva. Which of the following is the best initial treatment?

A. Topical corticosteroids

B. Topical oxacillin

C. Topical acyclovir

D. Oral idoxuridine

E. Topical trifluridine

Answer: A

Medical Abbreviations

AAA	abdominal aortic aneurysm
ABG	arterial blood gas
ACE	angiotensin-converting enzyme
ACTH	adrenocorticotropic hormone
ADH	antidiuretic hormone
AFB	acid-fast bacilli
Afib	atrial fibrillation
AIDS	acquired immune deficiency syndrome
AKI	acute kidney injury
ALS	amyotrophic lateral sclerosis
ANS	autonomic nervous system
ARB	angiotensin receptor blocker
ARDS	acute respiratory distress syndrome
ASA	aspirin
AST	aspartate transaminase
ALT	alanine transaminase
ANS	autonomic nervous system
ATP	adenosine triphosphate
AV	atrioventricular
AVM	arteriovenous malformation
BAL	bronchoalveolar lavage
BM	bowel movement
BMD	bone mineral density

(*Continued*)

BMI	body mass index
BP	blood pressure
BPH	benign prostatic hypertrophy
BSA	body surface area
BUN	blood urea nitrogen
C-ANCA	cytoplasmic antineutrophil cytoplasmic antibody
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CBC	complete blood count
CCB	calcium channel blocker
CF	cystic fibrosis
CHF	congestive heart failure
CKD	chronic kidney disease
CLL	chronic lymphocytic leukemia
CML	chronic myelogenous leukemia
CMV	cytomegalovirus
CN	cranial nerve
CNS	central nervous system
CO	carbon monoxide (or cardiac output)
COPD	chronic obstructive pulmonary disease
CPAP	continuous positive airway pressure
CPK	creatine phosphokinase
CPPD (also called pseudogout)	calcium pyrophosphate deposition
CPR	cardiopulmonary resuscitation
CSF	cerebrospinal fluid
CT	computed tomography
CVA	cerebrovascular accident
CVP	central venous pressure
DI	diabetes insipidus

DIC	disseminated intravascular coagulation
DLCO	diffusing capacity (of lung) for carbon monoxide
DM	diabetes mellitus
DOACs	direct oral anticoagulants
DO2	oxygen delivery
DTR	deep tendon reflexes
DVT	deep vein thrombosis
ECG	electrocardiogram
EEG	electroencephalogram
ED	emergency department
ERCP	endoscopic retrograde cholangiopancreatography
ESBL	extended spectrum beta-lactamases
ESR	erythrocyte sedimentation rate
FEVs	forced expiratory volumes
FNA	fine needle aspiration
FSH	follicle stimulating hormone
GERD	gastroesophageal reflux disorder
GI	gastrointestinal
GnRH	gonadotropin-releasing hormone
GU	genitourinary
HBsAg	hepatitis B surface antigen
Hct	hematocrit
HEENT	head, eyes, ears, nose, and throat
HIV	human immunodeficiency virus
HOCM	hypertrophic cardiomyopathy
HP	hypersensitivity pneumonitis
HRT	hormone replacement therapy

(*Continued*)

HR	heart rate (per minute)
HTN	hypertension
IBD	inflammatory bowel disease
IBS	irritable bowel syndrome
ICU	intensive care unit
IDDM	insulin-dependent diabetes mellitus
IGRA	interferon gamma release assay
IM	intramuscularly
IPF	idiopathic pulmonary fibrosis
IV	intravenously
IVC	interior vena cava
JVD	jugular venous distension
JVP	jugular venous pressure
LABAs	long-acting beta agonists (LABA)
LAMAs	long-acting muscarinic antagonists
LDH	lactate dehydrogenase
LFTs	liver function tests
LH	luteinizing hormone
LLL	left lower lobe
LLQ	left lower quadrant
LMP	last menstrual period
loc	loss of consciousness
LP	lumbar puncture
LUL	left upper lobe
LUQ	left upper quadrant
MI	myocardial infarction
MIBG scan	metaiodobenzylguanidine scan
MIC	minimum inhibitory concentration

MRI	magnetic resonance imaging
MRSA	methicillin-resistant *Staphylococcus aureus*
MS	multiple scleroris
MSSA	methicillin-sensitive *Staphylococcus aureus*
MVP	mitral valve prolapse (cardiology) or maximum vertical pocket (obstetrics)
NAAT	nucleic acid amplification test
NIDDM	non–insulin-dependent diabetes mellitus
NPH	normal pressure hydrocephalus
NSR	normal sinus rhythm
NST	non-stress test
NRTIs	nucleoside reverse transcriptase inhibitors
NSCLC	non-small-cell lung carcinoma
OCP	oral contraceptive pills
OSA	obstructive sleep apnea
OTC	over-the-counter
p-ANCA	perinuclear anti-neutrophil cytoplasmic antibodies
PA	posteroanterior
PAN	polyarteritis nodosa
PCP	primary care provider
PCP	*Pneumocystis carinii* pneumonia
PE	physical examination
PE	pulmonary embolus
PEEP	positive end-expiratory pressure
PERRLA	pupils are equal, round, and reactive to light and accommodation
PET	positron emission tomography
PF	pulmonary fibrosis
PFTs	pulmonary function tests

(*Continued*)

PID	pelvic inflammatory disease
PIs	protease inhibitors
PMI	point of maximum impulse
po	orally
POC	products of conception
pos	positive
PPD	packs per day
PPD	purified protein derivative
PRN	as needed
PSA	prostatic specific antigen
PT	prothrombin time
PTSD	post-traumatic stress disorder
PTT	partial prothrombin time
PUD	peptic ulcer disease
PVD	peripheral vascular disease
RA	rheumatoid arthritis
RBC	red blood cells
RDS	respiratory distress syndrome
RLL	right lower lobe
RLQ	right lower quadrant
RMG	rubs, murmurs, or gallops
ROM	range of motion
RR	respiratory rate
RRR	regular rate and rhythm
RUL	right upper lobe
RUQ	right upper quadrant
SAB	subarachnoid bleed
SABAs	short-acting beta agonists
SBO	small bowel obstruction

SCC	squamous cell carcinoma
SCFE	slipped capital femoral epiphysis
SCLC	small-cell lung carcinoma
SERM	selective estrogen receptor modulator
SH	social history
SHBG	sex hormone binding globulin
SJS	Stevens-Johnson Syndrome
SLE	systemic lupus erythematosus
SLR	straight leg raising
SOB	shortness of breath
SQ	subcutaneous
Staph	*Staphylococcus*
STD	sexually transmitted disease
Strep	*Streptococcus*
SV	stroke volume (per heartbeat)
T	temperature
TB	tuberculosis
TBB	transbronchial biopsy
TIA	transient ischemic attack
TMP/SMX	trimethoprim/sulfamethoxazole
TPPA	treponema pallidum particle agglutination
TSH	thyroid stimulating hormone
TURP	transurethral prostatectomy
U/A	urinalysis
UE	upper extremity
UIP	usual interstitial pneumonia
U/S	ultrasound
UTI	urinary tract infection

(*Continued*)

VATS	video-assisted thoracoscopic surgery
VCUG	voiding cystourethrogram
VDRL	Venereal Disease Research Laboratory
VMA	vanillylmandelic acid
WBC	white blood cells
WNL	within normal limits

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PART I

Obstetrics

Reproductive Basics 1

Learning Objectives

- ❑ Describe the basic physiology of spermatogenesis, ovulation, pregnancy, and lactation
- ❑ List the stages of fetal development and risks related to premature birth
- ❑ Answer questions about the terminology and epidemiology of perinatal statistics and genetic disorders detectable at birth

PLACENTAL HORMONES

Human Chorionic Gonadotropin

High-Yield

Human chorionic gonadotropin (hCG) is produced by the placental syncytiotrophoblast and first appears in maternal blood 10 days after fertilization. It peaks at 9–10 weeks and then gradually falls to a plateau level at 20–22 weeks.

By **chemical structure** hCG is a glycoprotein with 2 subunits. The α-subunit is similar to luteinizing hormone (LH), follicle-stimulating hormone (FSH), and thyrotropin (TSH). The β-subunit is specific for pregnancy.

The functions of hCG are as follows:

- **Maintain corpus luteum production** of progesterone until the placenta can take over maintenance of the pregnancy
- **Regulate steroid biosynthesis** in the placenta and fetal adrenal gland as well
- **Stimulate testosterone production** in the fetal male testes

If hCG levels are high, **twin pregnancy**, **hydatidiform mole**, choriocarcinoma, or embryonal carcinoma can occur. If levels are low, **ectopic pregnancy**, **threatened abortion**, or missed abortion can occur.

OB Triad

Human Chorionic Gonadotropin (hCG)

- Produced by syncytiotrophoblast
- Similar to LH, FSH, & TSH
- Maintains corpus luteum

Human Placental Lactogen

High-Yield

Human placental lactogen is chemically similar to anterior pituitary growth hormone and prolactin. Its level parallels placental growth, **rising throughout pregnancy**.

Its effect is to **antagonize** the cellular action of insulin, decreasing insulin utilization and thereby contributing to the predisposition of pregnancy to glucose intolerance and diabetes.

If levels are low, **threatened abortion or intrauterine growth restriction (IUGR)** can occur.

OB Triad

Human Placental Lactogen (hPL)

- Produced by syncytiotrophoblast
- Similar to HGH, prolactin
- Decreases insulin sensitivity

OB Triad

Progesterone

- Produced by corpus luteum
- Prepares endometrium for implantation
- Decreased myometrial contractility

Progesterone

High-Yield

Progesterone is a steroid hormone produced after ovulation by the luteal cells of the corpus luteum to induce endometrial secretory changes favorable for blastocyst implantation. It is initially produced exclusively by the corpus luteum for up to 6–7 menstrual weeks. Between 7–9 weeks, both the corpus luteum and the placenta produce progesterone. After 9 weeks the corpus luteum declines, and progesterone is exclusively produced by the placenta.

The functions of progesterone are as follows:

- **In early pregnancy** it induces endometrial secretory changes favorable for blastocyst implantation.
- **In later pregnancy** its function is to induce immune tolerance for the pregnancy and prevent myometrial contractions.

Estrogen

High-Yield

Estrogens are steroid hormones that occur in 3 forms. Each form has unique significance during a woman's life.

- **Estradiol** is the predominant moiety **during** the nonpregnant **reproductive years**. It is converted from androgens (produced from cholesterol in the follicular theca cells), which diffuse into the follicular granulosa cells containing the aromatase enzyme that completes the transformation into estradiol.
- **Estriol** is the main estrogen **during pregnancy**. Dehydroepiandrosterone-sulfate (DHEAS) from the fetal adrenal gland is the precursor for 90% of estriol converted by sulfatase enzyme in the placenta.
- **Estrone** is the main form **during menopause**. Postmenopausally, adrenal androstenedione is converted in peripheral adipose tissue to estrone.

Table I-1-1. Estrogens Throughout a Woman's Life

Estra*di*ol	Nonpregnant reproductive years	**Follicle** Granulosa
Est*ri*ol	Pregnancy	**Placenta** from fetal adrenal DHEAS
Est*rone*	After menopause	**Adipose** from adrenal steroids

PHYSIOLOGIC CHANGES IN PREGNANCY

Skin

- **Striae gravidarum:** "stretch marks" that develop in genetically predisposed women on the abdomen and buttocks
- **Spider angiomata** and **palmar erythema:** caused by increased skin vascularity
- **Chadwick sign:** bluish or purplish discoloration of the vagina and cervix caused by increased skin vascularity

- **Linea nigra:** increased pigmentation of the lower abdominal midline from the pubis to the umbilicus
- **Chloasma:** blotchy pigmentation of the nose and face

Cardiovascular

High-Yield

- **Arterial blood pressure:** Systolic and diastolic values both decline early in the first trimester, reaching a nadir by 24–28 weeks and then gradually rising toward term (but never returning quite to prepregnancy baseline). Diastolic falls more than systolic, as much as 15 mm Hg. Arterial blood pressure is **never normally elevated in pregnancy**.
- **Venous blood pressure:** Central venous pressure (CVP) is **unchanged with pregnancy**, but femoral venous pressure (FVP) increases two- to threefold by 30 weeks' gestation.
- **Plasma volume:** Plasma volume increases up to 50% with a significant increase by the first trimester. Maximum increase is by 30 weeks. This increase is even greater with multiple fetuses.
- **Systemic vascular resistance (SVR):** SVR equals blood pressure (BP) divided by cardiac output (CO). Because BP decreases and CO increases, SVR **declines** by 30%, reaching its nadir by 20 weeks. This enhances uteroplacental perfusion.
- **Cardiac output (CO):** CO **increases** up to 50%, with the major increase by 20 weeks. CO is the product of heart rate (HR) and stroke volume (SV), and both increase in pregnancy. HR increases by 20 beats/min by the third trimester. SV increases by 30% by the end of the first trimester.
  - CO is **dependent on maternal position**.
  - CO is **lowest** in the supine position because of inferior vena cava compression resulting in decreased cardiac return.
  - CO is **highest** in the left lateral position.
  - CO increases progressively through the three stages of labor.
- **Murmurs:** A systolic ejection murmur along the left sternal border is normal in pregnancy, owing to increased CO passing through the aortic and pulmonary valves. **Diastolic murmurs are never normal in pregnancy** and must be investigated.

Table I-1-2. Cardiovascular Changes

Arterial blood pressure	Systolic	↓
	Diastolic	↓↓
Venous pressure	Central	Unchanged
	Femoral	↑
Peripheral vascular resistance		↓

Hematologic

High-Yield

- **Red blood cell (RBC)** mass **increases** by 30% in pregnancy; thus, oxygen-carrying capacity increases. However, because plasma volume increases by 50% the calculated hemoglobin and hematocrit values decrease by 15%. The nadir of the hemoglobin value is at 28–30 weeks' gestation. **This is a physiologic dilutional effect, not a manifestation of anemia.**
- **White blood cell (WBC) count increases** progressively during pregnancy, with a mean value of up to 16,000/mm^3 in the third trimester.
- **Erythrocyte sedimentation rate (ESR) increases** in pregnancy because of the increase in gamma globulins.
- **Platelet count** normal reference range is **unchanged** in pregnancy.
- **Coagulation factors:** Factors V, VII, VIII, IX, XII, and von Willebrand factor **increase** progressively in pregnancy, leading to a hypercoagulable state.

Gastrointestinal

- **Stomach**: Gastric motility **decreases** and emptying time **increases** from the progesterone effect on smooth muscle. This increase in stomach residual volume, along with upward displacement of intraabdominal contents by the gravid uterus, predisposes to aspiration pneumonia with general anesthesia at delivery.
- **Large bowel**: Colonic motility **decreases** and transit time **increases** from the progesterone effect on smooth muscle. This predisposes to increased colonic fluid absorption, resulting in constipation.

Pulmonary

High-Yield

- **Tidal volume** (Vt), the volume of air that moves in and out of the lungs at rest, **increases** with pregnancy to 40%. It is the only lung volume that does not decrease with pregnancy.
- **Minute ventilation** ($\dot{V}e$) **increases** up to 40% with the major increase by 20 weeks. $\dot{V}e$ is the product of respiratory rate (RR) and Vt. RR remains unchanged, with Vt increasing steadily throughout the pregnancy into the third trimester.
- **Residual volume** (RV), the volume of air trapped in the lungs after deepest expiration, decreases up to 20% by the third trimester. This is largely due to the upward displacement of intraabdominal contents against the diaphragm by the gravid uterus.
- **Blood gases:** The rise in Vt produces a **respiratory alkalosis**, with a decrease in Pco_2 from 40 to 30 mm Hg and an increase in pH from 7.40 to 7.45. An increased renal loss of bicarbonate helps compensate, resulting in an alkalotic urine.

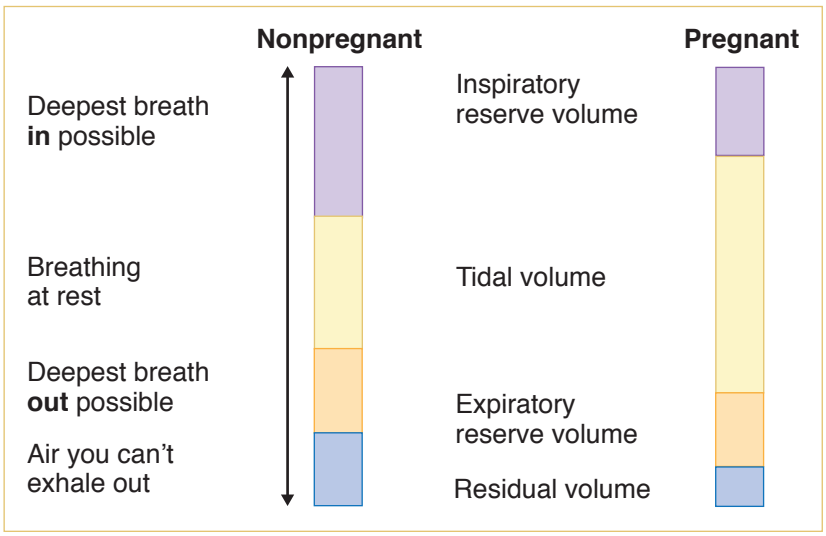


Figure I-1-1. Changes in Pulmonary System

Renal

High-Yield

- The **kidneys increase** in size 1.5 cm because of the increase in renal blood flow; this hypertrophy does not reverse until three months postpartum.
- **Ureteral** diameter **increases** owing to the progesterone effect on smooth muscle; the right side dilates more than the left in 90% of patients.
- **Glomerular filtration rate (GFR)**, renal plasma flow, and creatinine clearance all **increase** by 50% as early as the end of the first trimester; this causes a 25% decrease in serum blood urea nitrogen (BUN), creatinine, and uric acid.
- **Urine glucose** normally **increases**; glucose is freely filtered and actively reabsorbed, although the tubal reabsorption threshold falls from 195 to 155 mg/dL.
- **Urine protein** remains **unchanged**.

Endocrine

High-Yield

- **Pituitary** size **increases** up to threefold due to lactotroph hyperplasia and hypertrophy, making it susceptible to ischemic injury (Sheehan syndrome) from postpartum hypotension.
- **Adrenal** gland size is unchanged, but production of cortisol **increases** two- to threefold.
- **Thyroid** size remains **unchanged**; thyroid binding globulin (TBG) increases, resulting in **increased** total T_3 and T_4 (although free T_3 and free T_4 remain **unchanged**).

Fetal Circulation

High-Yield

Three **in utero shunts** exist within the fetus.

- **Ductus venosus** carries blood **from umbilical vein to the inferior vena cava**.
- **Foramen ovale** carries blood **from right to left atrium**.
- **Ductus arteriosus** shunts blood **from pulmonary artery to descending aorta**.

OB Triad

Fetal Circulation Shunts

- Ductus venosus (UV → IVC)
- Foramen ovale (RA → LA)
- Ductus arteriosus (PA → DA)

PHYSIOLOGY OF LACTATION

Anatomy

The breast is made of lobes of glandular tissue, with associated ducts for transfer of milk to the exterior and supportive fibrous and fatty tissue. On average, there are 15–20 lobes in each breast, arranged roughly in a wheel-spoke pattern emanating from the nipple area. The distribution of the lobes, however, is not even.

- There is a preponderance of glandular tissue in the upper outer portion of the breast (responsible for the tenderness in this region that many women experience prior to their menstrual cycle).
- About 80–85% of normal breast tissue is fat during the reproductive years. The 15–20 lobes are further divided into lobules containing alveoli (small saclike features) of secretory cells with smaller ducts that conduct milk to larger ducts and finally to a reservoir that lies just under the nipple. In the nonpregnant, nonlactating breast, the alveoli are small.
- During pregnancy, the alveoli enlarge; during lactation, the cells secrete milk substances (proteins and lipids). With the release of oxytocin, the muscular cells surrounding the alveoli contract to express the milk during lactation.
- Ligaments called **Cooper ligaments**, which keep the breasts in their characteristic shape and position, support breast tissue. In the elderly or during pregnancy, these ligaments become loose or stretched, respectively, and the breasts sag.
- The lymphatic system drains excess fluid from the tissues of the breast into the axillary nodes. Lymph nodes along the pathway of drainage screen for foreign bodies such as bacteria or viruses.

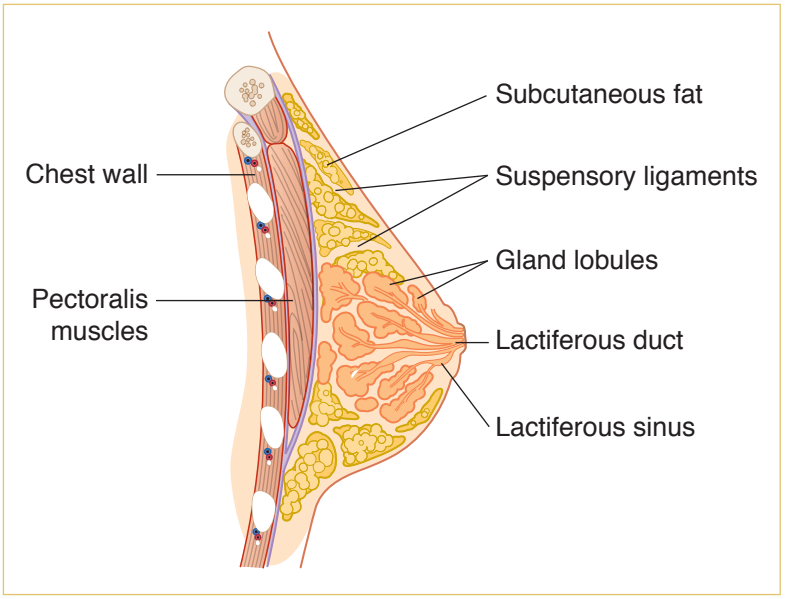


Figure I-1-2. Sagittal View of Breast

Hormones

Reproductive hormones are important in the development of the breast in puberty and in lactation.

- **Estrogen**, released from the ovarian follicle, promotes the growth ducts.
- **Progesterone**, released from the corpus luteum, stimulates the development of milk-producing alveolar cells.
- **Prolactin**, released from the anterior pituitary gland, stimulates milk production.
- **Oxytocin**, released from the posterior pituitary in response to suckling, causes milk ejection from the lactating breast.

Table I-1-3. Effect of Hormones on Breast

Estrogen	Ducts, nipples, fat
Progesterone	Lobules, alveoli
Prolactin	Milk production
Oxytocin	Milk ejection

Lactation

High-Yield

The breasts become fully developed under the influence of **estrogen**, **progesterone**, and **prolactin** during pregnancy. **Prolactin** causes the production of milk, and **oxytocin** release (via the suckling reflex) causes the contraction of smooth-muscle cells in the ducts to eject the milk from the nipple.

- The first secretion of the mammary gland after delivery is colostrum. It contains more protein and less fat than subsequent milk, and contains IgA antibodies which impart some **passive immunity** to the infant. Most often it takes one to three days after delivery for milk production to reach appreciable levels.
- The expulsion of the placenta at delivery initiates milk production and causes the drop in circulating estrogens and progesterone. **Estrogen** antagonizes the positive effect of prolactin on milk production.
- The physical stimulation of suckling causes the release of oxytocin and stimulates prolactin secretion, causing more milk production.

EMBRYOLOGY AND FETOLOGY

Embryonic and Fetal Development

Postconception week 1: most significant event is the **implantation of the blastocyst** on the endometrium.

Week 1 begins with fertilization of the egg and ends with implantation of the blastocyst onto the endometrial surface. Fertilization usually occurs in the distal part of the oviduct. The egg is capable of being fertilized for 12–24 hours. The sperm is capable of fertilizing for 24–48 hours. Week 1 can be divided into 2 phases:

- The **intratubal** phase extends through the first half of the first week. It begins at conception (day 0) and ends with the entry of the morula into the uterine cavity (day 3). The conceptus is traveling down the oviduct as it passes through the 2-cell, 4-cell, and 8-cell stages.

OB Triad

Post-Conception Week 1

- **Starts** at conception
- **Ends** with implantation
- **Yields** morula → blastula

- The **intrauterine** phase begins with entry of the morula into the uterus (day 3) and ends with implantation of the blastocyst onto the endometrial surface (day 6). During this time the morula differentiates into a hollow ball of cells. The outer layer will become the trophoblast or placenta, and the inner cell mass will become the embryo.

Postconception week 2: most significant event is the development of the **bilaminar germ disk with epiblast and hypoblast layers**. These layers will eventually give rise to the 3 primordial germ layers.

Another significant event is the invasion of the maternal sinusoids by the syncytiotrophoblast. Because β-human chorionic gonadotropin (β-hCG) is produced in the syncytiotrophoblast, this now allows β-hCG to enter the maternal bloodstream. **β-hCG pregnancy test now can be positive for the first time**.

Postconception week 3: most significant event is the migration of cells through the primitive streak between the epiblast and hypoblast to form the **trilaminar germ disk with ectoderm, mesoderm, and endoderm layers**. These layers will give rise to the major organs and organ systems.

Postconception weeks 4–8 (period of major teratogenic risk): during this time, the major organs and organ systems are being formed.

- **Ectoderm**: central and peripheral nervous systems; sensory organs of seeing and hearing; integument layers (skin, hair, and nails)
- **Mesoderm**: muscles, cartilage, cardiovascular system, urogenital system
- **Endoderm**: lining of the gastrointestinal and respiratory tracts

OB Triad

Post-Conception Week 2

- **Starts** with implantation
- **Ends** with 2-layer embryo
- **Yields** bi-laminar germ disk

OB Triad

Post-Conception Week 3

- **Starts** with 2-layer embryo
- **Ends** with 3-layer embryo
- **Yields** tri-laminar germ disk

OB Triad

Post-Conception Week 4–8

- Three germ layers differentiating
- Greatest risk of malformations
- Folic acid prevents NTD

Paramesonephric (Müllerian) Duct

This duct is present in all early embryos and is the primordium of the female internal reproductive system. **No hormonal stimulation is required.**

- In **males**, the Y chromosome induces gonadal secretion of müllerian inhibitory factor (MIF), which causes the müllerian duct to involute.
- In **females**, without MIF, development continues to form the fallopian tubes, corpus of the uterus, cervix, and proximal vagina.

Female External Genitalia

No hormonal stimulation is needed for differentiation of the external genitalia into labia majora, labia minora, clitoris, and distal vagina.

Mesonephric (Wolffian) Duct

This duct is also present in all early embryos and is the primordium of the male internal reproductive system. **Testosterone stimulation is required** for development to continue to form the vas deferens, seminal vesicles, epididymis, and efferent ducts. This is present in males from testicular sources. In females, without androgen stimulation, the Wolffian duct undergoes regression. If a genetic male has an absence of androgen receptors, the Wolffian duct will also undergo regression.

Male External Genitalia

Dihydrotestosterone (DHT) stimulation is needed for differentiation of the external genitalia into a penis and scrotum. If a genetic male has an absence of androgen receptors, external genitalia will differentiate in a female direction.

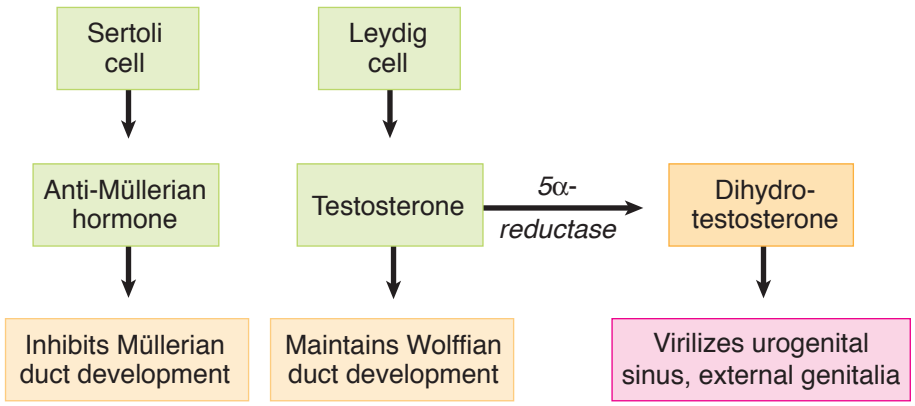


Figure I-1-3. Testicular Function

Table I-1-4. Hormones

Hormones Needed for Genital Development		
♀	External?	None
	Internal?	
♂	External?	Androgen
	Internal?	

Table I-1-5. Embryology

Primordia	Female	Male	Major Determinant Factors
Gonadal			
Germ cells Coelomic epithelium Mesenchyme Mesonephros	Oogonia Granulosa cells Theca cells Rete ovarii	Spermatogonia Sertoli cells Leydig cells Rete testis	Sex chromosomes
Ductal			
Paramesonephric (Müllerian) Mesonephric (Wolffian) Mesonephric tubules	Fallopian tubes Uterus Part of vagina Gartner's duct Epoophoron Paroophoron	Testis hydatid Vas deferens Seminal vesicles Epididymis Efferent ducts	Absence of Y chromosome Testosterone Müllerian-inhibiting factor
External Genitalia			
Urogenital sinus Genital tubercle Urogenital folds Genital folds	Vaginal contribution Skene's glands Bartholin's glands Clitoris Labia minora Labia majora	Prostate Bulbourethral glands Prostatic utricle Penis Corpora spongiosa Scrotum	Presence or absence of testosterone, dihydrotestosterone, and 5-alpha reductase enzyme

Teratology

A 36-year-old woman undergoes a barium enema for rectal bleeding on February 1, with estimated radiation dose of 4 rad. Her last menstrual period (LMP) was January 1 and she has 35-day cycles. She was not using any contraception. On March 15, a urine pregnancy test is positive. She inquires about the risk to her fetus of teratogenic injury.

A teratogen is any agent that disturbs normal fetal development and affects subsequent function. The nature of the agent, as well as its timing and duration after conception, is critical. There are critical periods of susceptibility with each teratogenic agent and with each organ system.

The **stages** of teratogenesis are as follows:

- **From conception to end of second week:** embryo either survives intact or dies because the three germ layers have not yet been formed
- **Postconception weeks 3–8:** period of greatest teratogenic risk from formation of the three germ layers to completion of organogenesis
- **After week 9 of postconception:** teratogenicity is low but adverse effects may include diminished organ hypertrophy and hyperplasia

The **types** of agents that can result in teratogenesis or adverse outcomes are as follows:

- **Infectious:** Agents include bacteria (e.g., chlamydia and gonorrhea cause neonatal eye and ear infections), viruses (e.g., rubella, cytomegalovirus, herpes virus), spirochetes (e.g., syphilis), and protozoa (e.g., toxoplasmosis).
- **Ionizing radiation:** No single diagnostic procedure results in radiation exposure to a degree that would threaten the developing pre-embryo, embryo, or fetus. No increase is seen in fetal anomalies or pregnancy losses with exposure of <5 rads. The greatest risk of exposure is between 8 and 15 weeks' gestation with the risk of nonthreshold, linear function at doses of at least 20 rads.
- **Chemotherapy:** Risk is predominantly a first-trimester phenomenon. Second- and third-trimester fetuses are remarkably resistant to chemotherapeutic agents.
- **Environmental:** Tobacco is associated with intrauterine growth restriction (IUGR) and preterm delivery, but no specific syndrome. Alcohol is associated with fetal alcohol syndrome: midfacial hypoplasia, microcephaly, intellectual disability, and IUGR.
- **Recreational drugs:** Cocaine is associated with placental abruption, preterm delivery, intraventricular hemorrhage, and IUGR. Marijuana is associated with preterm delivery but not with any syndrome.
- **Medications** (account for 1–2% of congenital malformations): The ability of a drug to cross the placenta to the fetus depends on molecular weight, ionic charge, lipid solubility, and protein binding. Drugs are listed by the FDA as category A, B, C, D, or X.

FDA Pregnancy Risk Categories

High-Yield

Prior to 2015

- **Category A:** adequate and well-controlled studies have **failed** to demonstrate a risk to the fetus. **Okay to use.** Examples include levothyroxine, folic acid, liothyronine.

- **Category B:** animal studies have **failed** to demonstrate a risk to the fetus but there are no good studies in pregnant women. **Okay to use.** Examples include metformin, hydrochlorothiazide, cyclobenzaprine, amoxicillin, pantoprazole.
- **Category C:** animal studies have shown an **adverse effect** on the animal fetus; there are no good studies in humans but **potential benefits** may warrant use of the drug in pregnant women. **May use.** Examples include tramadol, gabapentin, amlodipine, trazodone.
- **Category D:** human studies have shown an **adverse effect** on human fetus but **potential benefits** may warrant use of the drug in pregnant women. **May use.** Examples include lisinopril, alprazolam, losartan, clonazepam, lorazepam.
- **Category X:** human studies have shown an **adverse effect** on human fetus and **risks clearly outweigh benefits** in pregnant women. **Do not use.** Examples include atorvastatin, simvastatin, warfarin, methotrexate, finasteride.

After 2015

The A, B, C, D, and X risk categories in use since 1979 have now been replaced with **narrative sections** and subsections to include **pregnancy** (includes labor and delivery), lactation (includes nursing mothers), and **females and males of reproductive potential**.

While the new labeling improves the old format, it still does not provide a definitive "yes or no" answer in most cases. Clinical interpretation is still required on a case-by-case basis.

The **Pregnancy** subsection will provide information about dosing and potential risks to the developing fetus, and **registry information** that collects and maintains data on how pregnant women are affected when they use the drug or biological product.

Specific Syndromes

High-Yield

- **Alcohol:** fetal alcohol syndrome—IUGR, **midfacial hypoplasia**, developmental delay, short palpebral fissures, **long philtrum**, multiple joint anomalies, cardiac defects
- **Diethylstilbestrol:** DES syndrome—**T-shaped uterus**, **vaginal adenosis** (with predisposition to **vaginal clear cell carcinoma**), cervical hood, incompetent cervix, preterm delivery
- **Dilantin:** fetal hydantoin syndrome—IUGR, **craniofacial dysmorphism** (epicanthal folds, depressed nasal bridge, oral clefts), **intellectual disability**, **microcephaly**, nail hypoplasia, heart defects
- **Isotretinoin (Accutane): congenital deafness**, **microtia**, CNS defects, congenital heart defects
- **Lithium: Ebstein's anomaly** (right atrial enlargement and downward displacement of tricuspid valve)
- **Streptomycin:** VIII nerve damage, hearing loss
- **Tetracycline:** after fourth month, deciduous teeth discoloration
- **Thalidomide: phocomelia**, **limb reduction defects**, ear/nasal anomalies, cardiac defects, pyloric or duodenal stenosis
- **Trimethadione: facial dysmorphism** (short upturned nose, slanted eyebrows), cardiac defects, IUGR, intellectual disability
- **Valproic acid: neural tube defects** (spina bifida), cleft lip, renal defects
- **Warfarin: chondrodysplasia** (stippled epiphysis), microcephaly, intellectual disability, optic atrophy

PERINATAL STATISTICS AND TERMINOLOGY

Table I-1-6. Terminology for Perinatal Statistics

Terminology	Definition
Gravidity	Total number of pregnancies irrespective of the pregnancy duration
Nulligravida	Woman who is not currently pregnant and has never been pregnant
Primigravida	Woman who is pregnant currently for the first time
Multigravida	Woman who is pregnant currently for more than the first time
Parity	Total number of pregnancies achieving ≥20 weeks' gestation
Nullipara	Woman who has never carried a pregnancy achieving ≥20 weeks' gestation
Primipara	Woman who has carried one pregnancy achieving ≥20 weeks' gestation
Multipara	Woman who has carried more than one pregnancy to ≥20 weeks' gestation
Parturient	Woman who is in labor
Puerpera	Woman who has just given birth

Table I-1-7. Terminology for Perinatal Losses

Terminology	Definition
Abortion	Pregnancy loss prior to 20 menstrual weeks
Antepartum death	Fetal death between 20 menstrual weeks and onset of labor
Intrapartum death	Fetal death from onset of labor to birth
Fetal death	Fetal death between 20 menstrual weeks and birth
Perinatal death	Fetal/neonatal death from 20 menstrual weeks to 28 days after birth
Neonatal death	Newborn death between birth and the first 28 days of life
Infant death	Infant death between birth and first year of life
Maternal death	A woman who died during pregnancy or within 90 days of birth

Table I-1-8. Terminology for Mortality Rates

Terminology	Definition
Birth rate	Number of live births per 1,000 total population
Fertility rate	Number of live births per 1,000 women ages 15–45 years
Fetal mortality rate	Number of fetal deaths per 1,000 total births
Neonatal mortality rate	Number of neonatal deaths per 1,000 live births
Perinatal mortality rate	Number of fetal + neonatal deaths per 1,000 total births
Infant mortality rate	Number of infant deaths per 1,000 live births
Maternal mortality ratio	Number of maternal deaths per 100,000 live births

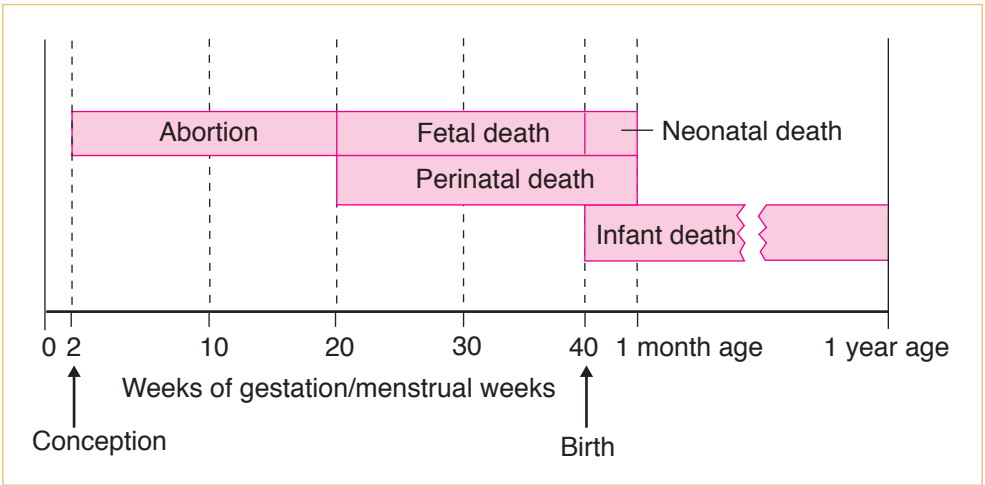


Figure I-1-4. Perinatal Mortality Terminology

GENETIC DISORDERS

Human Genetics in Pregnancy

A 37-year-old G5 P0 Ab4 comes for prenatal care at 7 weeks' gestation. She has experienced four previous spontaneous first-trimester abortions. She is concerned about the likelihood of her next pregnancy being successful.

Indicators for genetic counseling during pregnancy include the following:

- **Advanced maternal age:** women age ≥35 at increased risk of fetal nondisjunction trisomies (e.g., trisomies 21 and 18)
- **Incidence of chromosomal abnormalities by maternal age: the greater the age, the greater the risk**
- **Multiple fetal losses**
- **Previous child:** neonatal death, intellectual disability, aneuploidy, known genetic disorder
- **Pregnancy or fetal losses:** stillborn with birth defect, multiple pregnancy, or fetal losses
- **Family history:** genetic diseases, birth defects, intellectual disability,
- **Abnormal prenatal tests:** triple marker screen, sonogram
- **Parental aneuploidy**

Chromosomal Aberrations

High-Yield

Note

Trisomy: extra single, 47,XX+21

Monosomy: missing single, 45,X

Polyploidy: extra set, 69,XXY

- **Aneuploidy** refers to **numeric chromosome abnormalities** in which cells contain other than 2 complete sets of 23 chromosomes. This usually occurs because of **nondisjunction**.
  - The **most common** aneuploidy is **trisomy**, the presence of an extra chromosome.
  - Most autosomal trisomies result in spontaneous abortion.
  - The **most common** trisomy in first-trimester losses is trisomy 16.
  - The **most common** trisomy at term is trisomy 21.
- **Polyploidy** refers to numeric chromosome abnormalities in which cells contain complete **sets of extra chromosomes**. The most common polyploidy is **triploidy** with 69 chromosomes, followed by **tetraploidy** with 92 chromosomes. An example of triploidy is an **incomplete molar** pregnancy, which occurs from fertilization of an egg by two sperm.
- **Structural alteration** refers to a condition in which chromosomal material is deleted, gained, or rearranged. It can involve single or multiple chromosomes. An example of a chromosomal deletion is del (5p) or cri du chat syndrome, which is a deletion of the short arm of chromosome 5.
- **Mosaicism** refers to the presence of ≥2 cytogenetically distinct cell lines in the same individual. Mosaicism can involve the placentae, the fetus, or both. Gonadal mosaicism can result in premature **ovarian failure** and predispose the gonad to **malignancy**.

Translocations

High-Yield

- **Reciprocal translocation** involves any 2 or more nonhomologous chromosomes and occurs when there is a **breakage and reunion** of portions of the involved chromosomes to yield new products. Carriers of **balanced reciprocal translocations** have 46 chromosomes, with both derivative chromosomes present. Offspring may also have 46 chromosomes but only one of the derivative chromosomes is present.

- **Robertsonian translocation** always involves the **acrocentric chromosomes** and is caused by centric fusion after loss of the satellite region of the short arms of the original acrosomic chromosome. The karyotype of a balanced Robertsonian translocation will appear to have only 45 chromosomes; however, the full complement of genetic material is present, and there are no clinical effects. The offspring may have 46 chromosomes but have double the genetic material of a particular chromosome.

Cytogenetic Disorders

High-Yield

At least 50% of first-trimester abortuses have abnormal chromosomes. The 2 **most common aneuploidies in miscarriage** are trisomy 16 and monosomy X (50% of these abnormalities are autosomal trisomies, with trisomy 16 the most common).

- **Turner syndrome (45,X)** (also known as **gonadal dysgenesis** or **monosomy X**) (1 in 2,000 births) is most often the result of loss of the paternal X chromosome; 98% of these conceptions abort spontaneously. Obstetric ultrasound shows the characteristic nuchal skin-fold thickening and cystic hygroma. Those fetuses that do survive to term have the following:
  - Absence of secondary sexual development
  - Short stature
  - Streak gonads
  - Primary amenorrhea/primary infertility
  - Broad chest
  - Neck webbing
  - Urinary tract anomalies
  - Bicuspid aortic valve and aortic coarctation
  - Normal intelligence
  - Possible mosaic patterns, with ovarian follicles present
- **Klinefelter syndrome (47,XXY)** (1 in 1,000 births) is seldom diagnosed before puberty. Physical findings include tall stature, testicular atrophy, azoospermia, gynecomastia, and truncal obesity. Learning disorders, autoimmune diseases, and low IQ are common.
- **Down syndrome (trisomy 21)** (1 in 800 births) accounts for 50% of all cytogenetic diseases at term. IUGR and polyhydramnios are common. T21 incidence increases with advancing maternal age. The syndrome is characterized by intellectual disability, short stature, muscular hypotonia, brachycephaly, and short neck. Typical facial appearance is oblique orbital fissures, flat nasal bridge, small ears, nystagmus, and protruding tongue. Congenital heart disease (**endocardial cushion defects**) is more common along with **duodenal atresia**.

OB Triad

Turner Syndrome

- Primary amenorrhea
- Web neck
- Streak gonads

OB Triad

Klinefelter Syndrome

- Testicular atrophy
- Gynecomastia
- Azoospermia

OB Triad

Down Syndrome

- Short stature
- Intellectual disability
- Endocardial cushion cardiac defects

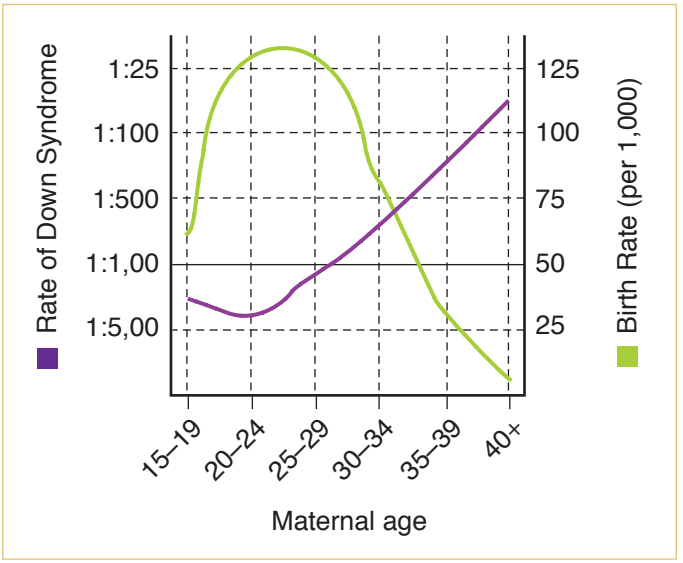


Figure I-1-5. Birth Rate and Rate of Down Syndrome versus Maternal Age

- **Edward syndrome (trisomy 18)** (1 in 5,000 births) is more frequent with advancing maternal age; 80% of cases occur in females. IUGR is common. It is associated with profound intellectual disability. Unique findings are rocker-bottom feet and clenched fists. Survival to age 1 year is <10%, with mean survival 14 days.
- **Patau syndrome (trisomy 13)** is more frequent with advancing maternal age. It is associated with profound intellectual disability. Associated findings include IUGR, cyclopia, proboscis, holoprosencephaly, and severe cleft lip with palate. Survival to age 1 year is rare, with mean survival 2 days.

Table I-1-9. Genetic Syndromes

Name	Karyotype	Stature	IQ	Unique Finding
Klinefelter	47,XXY	Tall	Decreased IQ	Microgenitals, infertility
Turner	45,X	Short	Normal IQ	Web neck, coarctation aorta
Down	T21	Short	Functional intellectual disability	Duodenal atresia, AV canal defect
Edward	T18	Short	Severe intellectual disability	Abnormal feet, fist
Patau	T13	Short	Profound intellectual disability	Holoprosencephaly, cyclops

Mendelian Disorders

High-Yield

A 23-year-old black primigravida is seen at 12 weeks' gestation. She has been diagnosed with sickle cell trait (AS). Her husband and father of the baby is also AS. She inquires as to the risk of her baby having sickle cell disease (SS).

About **1%** of liveborn infants have a congenital Mendelian disorder. About **15%** of all birth defects are attributable to Mendelian disorders; of these, **70%** are autosomal dominant. The remainder are autosomal recessive or X-linked.

Autosomal dominant

Transmission occurs equally to males and females, and serial generations are affected. **Gross anatomic abnormalities are the most common findings.** Age of onset is usually delayed, with variability in clinical expression.

Each affected individual has an affected parent (unless this is a new mutation). Affected individuals will transmit the disease to 50% of their offspring. Unaffected individuals will bear unaffected children (if penetrance is complete). **There are no carrier states.**

Autosomal dominant examples include the following:

Polydactyly	Marfan syndrome	Neurofibromatosis
Huntington chorea	Myotonic dystrophy	Osteogenesis imperfecta
Achondroplasia	Polycystic kidneys	

Autosomal recessive

Transmission occurs equally to males and females, but the disease often skips generations. **Enzyme deficiencies are most common findings**. Age of onset is usually earlier with consistency in clinical expression. **Carrier states are common.**

- If both parents are heterozygous for the gene, 25% of offspring will be affected, 50% will be carriers, and 25% will be normal.
- If one parent is homozygous and one is heterozygous, 50% of offspring will be affected, and 50% will be carriers.
- If both parents are homozygous, 100% of children will be affected.
- **Carrier states are common.**

Autosomal recessive examples include the following:

Deafness	Albinism	Phenylketonuria
Congenital adrenal hyperplasia	Sickle cell anemia	Cystic fibrosis
Thalassemia	Tay-Sachs disease	Wilson disease

OB Triad

Autosomal Recessive

- Transmitted by both sexes
- Often skips generations
- Male and female carriers

OB Triad

X-Linked Recessive

- No male–male transmission
- Expressed only in males
- Female carriers

X-linked recessive

These conditions are functionally dominant in men, but may be dominant or recessive in women. There is no male-to-male transmission (because the father gives only his Y chromosome to his son), but transmission is 100% male to female. The usual transmission is from heterozygous females to male offspring in an autosomally dominant pattern.

The disease is expressed in all males who carry the gene. Family history reveals the disorder is only found in male relatives, and commonly in maternal uncles.

X-linked recessive examples include:

Hemophilia A	Diabetes insipidus
Color blindness	Hydrocephalus
Complete androgen insensitivity	Duchenne muscular dystrophy

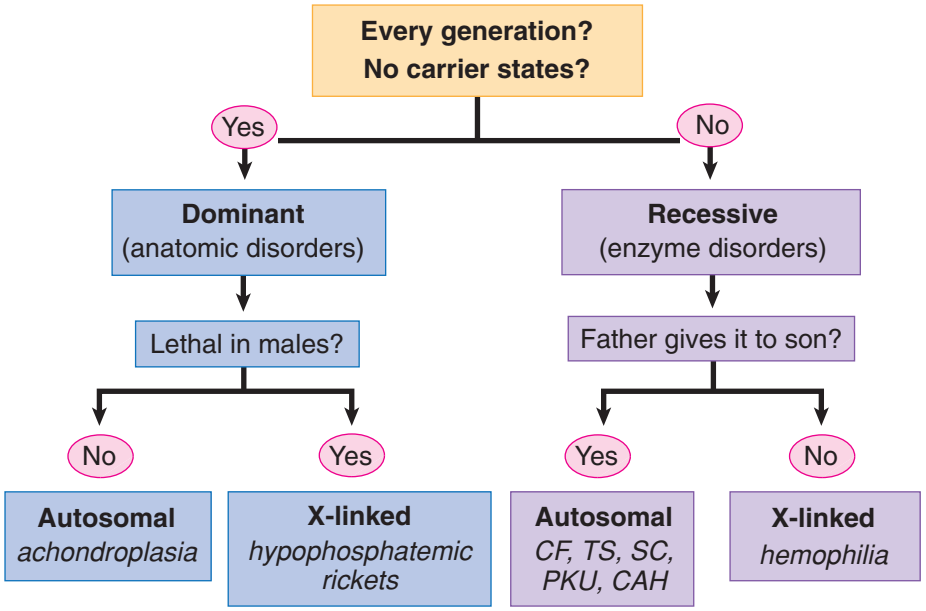
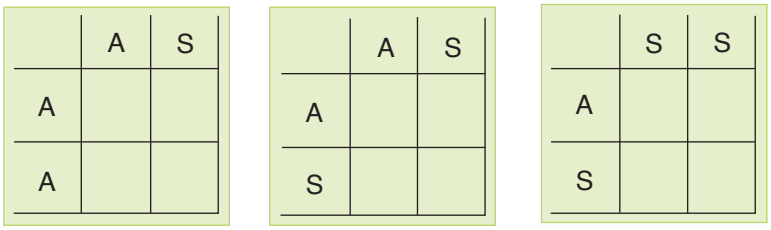


Figure I-1-6. Mendelian Genetics

X-linked dominant

These conditions may show up as two types of disorders:

- Manifested in female heterozygotes as well as carrier males (hemizygotes), e.g., hypophosphatemic rickets
- Manifested in female heterozygotes but lethal in males (the increased spontaneous abortion rate represents male fetuses), e.g., incontinentia pigmenti, focal dermal hypoplasia, orofaciodigital syndrome



Calculations of Autosomal Recessive Risk

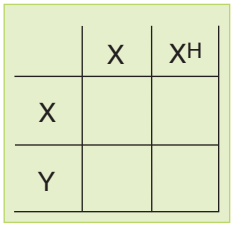


Figure I-1-7. Calculations of X-linked Risk (Hemophilia)

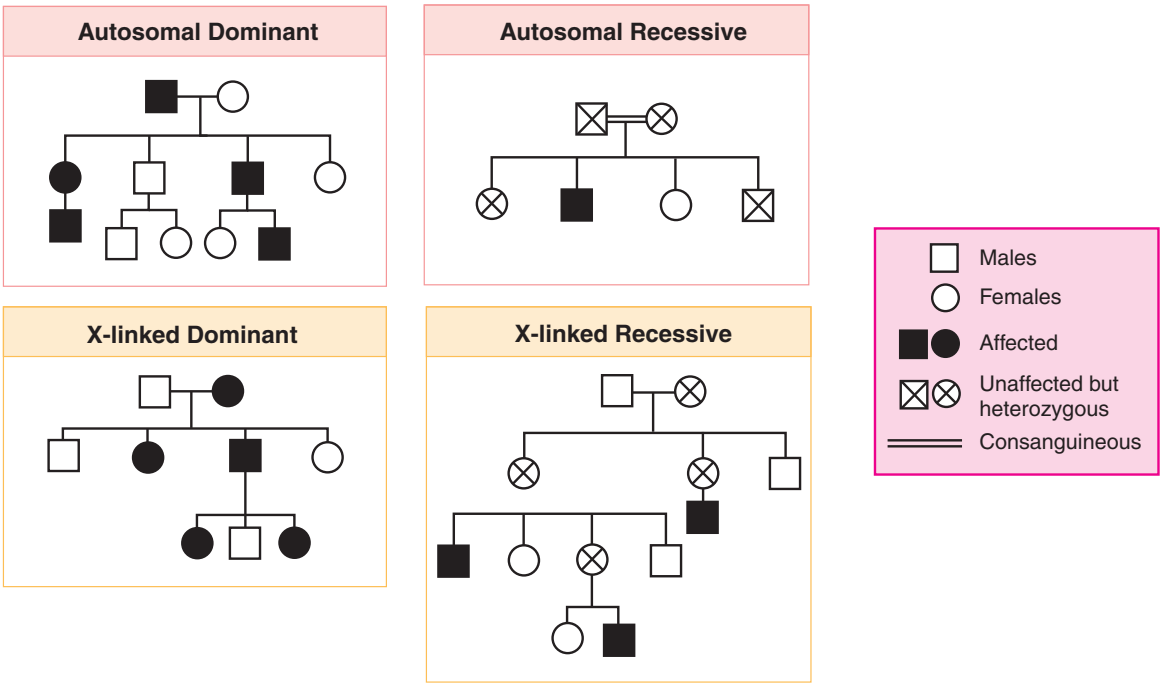


Figure I-1-8. Familial Transmission Patterns of Inheritance

Multifactorial Disorders

High-Yield

A 32-year-old woman with corrected tetralogy of Fallot is pregnant at 18 weeks' gestation with a male fetus. She inquires as to the chance that her son has congenital heart disease.

The majority of birth defects (70%) are multifactorial or polygenic in origin, which means there is an **interaction of multiple genes with environmental factors**. Characteristic Mendelian patterns are not found, but there is an increased frequency of the disorder or phenotype in families. **Overall recurrence rate is 2–3%.**

- As the number of genes for a multifactorial trait increases, the liability for the disease increases.
- The more severe the malformation, the higher the risk for recurrence.

Examples of multifactorial inheritance include the following:

Neural tube defects	Cleft lip and palate
Congenital heart disease	Pyloric stenosis

- **Neural tube defects** (NTD) (1–2 per 1,000 births): The spectrum ranges from anencephaly to very slight vertebral defects. Result from failure of neural tube closure by **day 22–28 postconception**. Anencephaly and spina bifida occur with equal frequency. Polyhydramnios is frequently seen.
  - Women at high risk for NTD should take **4 mg** of folic acid. **Preconception folic acid supplementation** may decrease incidence of NTD.
  - All women should take **0.4 mg** of folic acid.
- **Congenital heart disease** (CHD) (1% of births): The majority of isolated CHD are multifactorial **with an overall recurrence risk of 2%**. However, the specific recurrence risk depends on the defect and family history details. It is important to distinguish isolated defects from those that are part of a syndrome with a higher recurrence risk. Preconception folate reduces the risk of congenital CHD, as well as NTD.
- **Cleft lip and palate** (1 per 1,000 births): The risk of cleft lip in a second child of unaffected parents is 4%. If two children are affected, the risk of the third child being affected is 10%.
- **Pyloric stenosis (more common in males)**: The risk of the condition in the offspring of an affected parent is much greater if that parent is female.

Failed Pregnancy 2

Learning Objectives

- ❑ Describe the detection and risks of ectopic pregnancy
- ❑ List the approaches to induced abortion at different stages of fetal development
- ❑ Describe the epidemiology and management of early pregnancy bleeding and fetal demise

INDUCED ABORTION

Nearly 50% of all pregnancies among American women are unintended, and 4 in 10 of these are terminated by abortion. Excluding miscarriages, 25% of all pregnancies end in abortion.

- Early first-trimester abortions pose virtually no long-term risk of infertility, ectopic pregnancy, spontaneous abortion (miscarriage), or congenital malformation (birth defect), and little or no risk of preterm or low birthweight deliveries. Very few abortion patients experience a complication that requires hospitalization.
- Numerous epidemiologic studies have shown no association between abortion and breast cancer or any other type of cancer.
- The risk of maternal death associated with abortion increases with advancing gestational age. The maternal mortality associated with childbirth is about 12 times as high as that associated with early first-trimester abortion.

First-Trimester Methods

High-Yield

- **Vacuum curettage** (dilation and curettage [D&C]) (**most common abortion** procedure in the United States at 90%) is performed before 13 weeks' gestation. Prophylactic antibiotics are given to reduce the infection rate, and conscious sedation and paracervical block local anesthetic are administered for pain relief.
  - The cervical canal is dilated with tapered metal cervical dilators or hygroscopic/osmotic dilators such as **laminaria**.
  - Complications are rare but include endometritis (treated with outpatient antibiotics) and retained products of conception (POC) (treated with repeat curettage).
  - Maternal mortality ratio: **1 per 100,000** women.
- **Medical abortion: Mifepristone** has been marketed over the past decade as an alternative to surgical abortion. Medical induction of abortion can be induced using oral mifepristone (a **progesterone antagonist**) and oral misoprostol (prostaglandin E1). Use is limited to the first 63 days of amenorrhea.
  - Approximately 85% of patients will abort within three days. The earlier the gestational age, the higher the success rate. About 2% of patients abort incompletely and require vacuum curettage.
  - Rare cases of ***Clostridium sordellii*** sepsis have been reported.

Second-Trimester Methods

High-Yield

The more advanced the gestation, the higher the rate of complications.

- **Dilation and evacuation** (D&E) (**most common second-trimester abortion** procedure): Cervical dilation is performed by inserting osmotic laminaria dilators 24 hours prior to the procedure. The **cervical dilation in millimeters equals the number of weeks of gestation** (e.g., at 18 weeks, the cervix should be dilated 18 mm).
  - Early second-trimester abortions (13–14 weeks) can be performed by vacuum aspiration. After 14 weeks, the fetus is morcellated and removed in pieces. Ultrasound guidance can ensure complete evacuation of pregnancy tissues. A D&E is difficult to perform after 20 weeks due to toughness of fetal tissues.
  - An **intact D&E** involves more advanced pregnancies, with ≥2 days of laminaria treatment to obtain wide cervical dilation, allowing assisted breech delivery of the fetus under ultrasound guidance and decompression of the calvaria; the fetus is otherwise delivered intact (sometimes referred to as "partial birth" abortion). An intact D&E can be performed up to 24 weeks.
  - Pain relief is achieved through local, intravenous, or spinal anesthesia.
  - **Immediate complications** may include uterine perforation, retained tissue, hemorrhage, infection, and, rarely, disseminated intravascular coagulation. **Delayed complications** may include cervical trauma with resulting cervical insufficiency. Maternal mortality ratio is **4 per 100,000** women.
- **Labor induction methods:** Stimulation of **uterine contractions** to dilate the cervix can be achieved with **prostaglandins** (intra-amniotic $PGF_{2\alpha}$), vaginal PGE_2 (dinoprostone), IM 15-methyl $PGF_{2\alpha}$ (carboprost tromethamine), or PGE_1 (misoprostol). Interval from induction to delivery may be up to 24 hours.
  - Delivery of a live fetus may occur with use of prostaglandin (PG) analogs; feticidal agents used include intracardiac injection of KCl or digoxin.
  - **Immediate complications** include retained placentae (the most common problem with all PG abortions), hemorrhage, and infection. **Delayed complications** include cervical trauma with resulting cervical insufficiency. Maternal mortality ratio is **8 per 100,000** women.

Table I-2-1. Methods of Induced Abortion

Trimester	Method	Procedure	Maternity-Mortality Ratio
First Trimester	Surgical	Suction dilation & curettage (D&C)	1
	Medical	Mifepristone (progesterone antagonist)	1
Second Trimester	Surgical	Dilation & evacuation (D&E)	4
	PGE_1	Induction of labor contractions	8
Any Trimester	Major surgery	Hysterotomy, hysterectomy	25

EARLY PREGNANCY BLEEDING

A 40-year-old woman (G3 P1 Ab1) at 9 weeks' gestation comes to the office complaining of vaginal bleeding. A urine pregnancy test was positive 3 weeks ago. She initially experienced breast tenderness, though it has now disappeared. She denies passage of any tissue vaginally.

Early pregnancy bleeding is bleeding that occurs before 12 weeks' gestation. The most common cause of early pregnancy loss is fetal in origin.

- **Cytogenetic etiology:** Most early pregnancy losses are caused by gross chromosomal abnormalities of the embryo or fetus.
- **Mendelian etiology:** Other losses may be caused by autosomal or X-linked dominant or recessive diseases.
- **Antiphospholipid syndrome:** An uncommon cause of early pregnancy loss. Some women with SLE produce antibodies against their own vascular system and fetoplacental tissues. Treatment is subcutaneous heparin.

Clinical Findings: Speculum exam is essential to rule out vaginal or cervical lesions that are causing bleeding.

- **RhoGAM** should be administered to all Rh-negative gravidas who undergo dilatation and curettage (D&C).
- **Molar** and **ectopic pregnancy** should be ruled out in all patients with early pregnancy bleeding.

Clinical Entities

High-Yield

The following diagnoses represent findings along a continuum, from the beginnings of losing the pregnancy to complete expulsion of the products of conception (POC).

- **Missed abortion:** sonogram finding of a nonviable pregnancy without vaginal bleeding, uterine cramping, or cervical dilation. **Management:** Scheduled suction D&C, conservative management awaiting a spontaneous completed abortion, or induce contractions with misoprostol (PGE 1).
- **Threatened abortion:** sonogram finding of a viable pregnancy with vaginal bleeding but no cervical dilation (50% of these pregnancies will continue to term successfully). **Management:** Often the cause is implantation bleeding. Observation. No intervention is generally indicated or effective.
- **Inevitable abortion:** vaginal bleeding and uterine cramping leading to cervical dilation, but no POC has yet been passed. **Management:** Emergency suction D&C if bleeding is heavy to prevent further blood loss and anemia. Otherwise, conservative management awaiting a spontaneous completed abortion or induce contractions with misoprostol PGE 1.
- **Incomplete abortion:** vaginal bleeding and uterine cramping leading to cervical dilation, with some, but not all, POC having been passed. **Management:** Emergency suction D&C if bleeding is heavy to prevent further blood loss and anemia. Otherwise conservative management awaiting a spontaneous completed abortion or induce contractions with misoprostol PGE 1.

Note

For more discussion about antiphospholipid syndrome, see Thrombophilias section in chapter 10.

- **Completed abortion:** vaginal bleeding and uterine cramping have led to all POC being passed. This is confirmed by a sonogram showing no intrauterine contents or debris. **Management:** Conservative if an intrauterine pregnancy had been previously confirmed. Otherwise, serial β-human chorionic gonadotropin (β-hCG) titers should be obtained weekly until negative to ensure an ectopic pregnancy has not been missed.

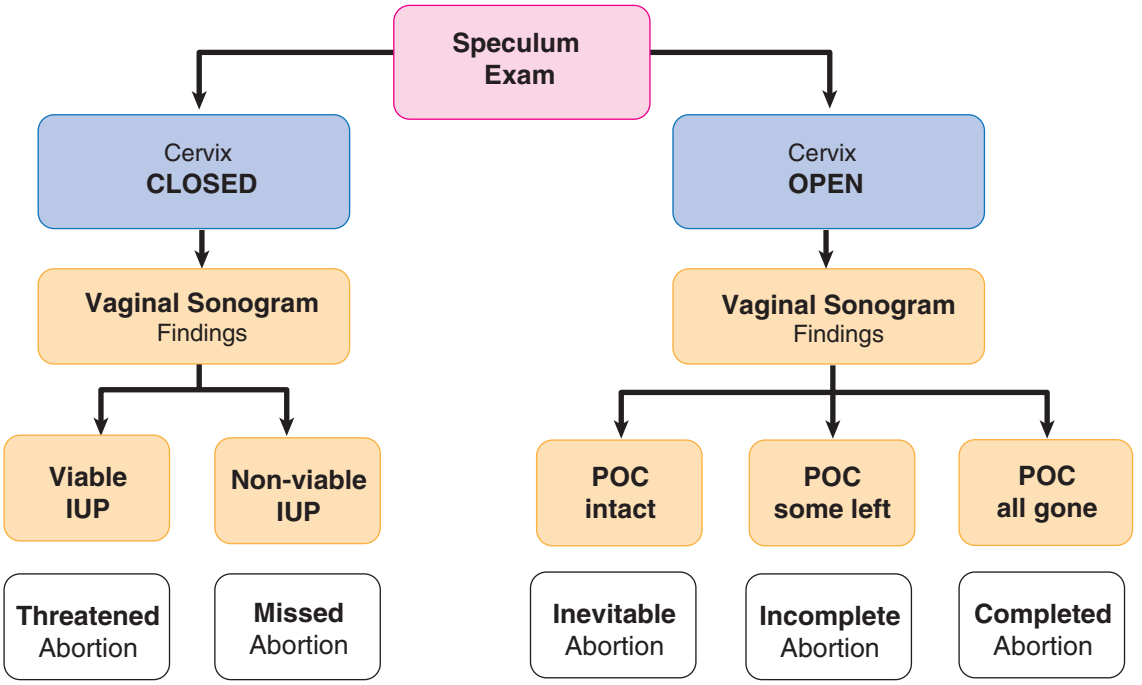


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Figure I-2-1. Approach to Early Pregnancy Bleeding

FETAL DEMISE

A 28-year-old multigravida at 33 weeks' gestation comes to the office stating she has not felt her baby move for 24 hours. A previous 18-week sonogram showed a single fetus with grossly normal anatomy. You are unable to find fetal heart tones by auscultation with a Doppler stethoscope.

From a medical viewpoint, fetal demise applies to any death after the embryo period (**≥10 menstrual weeks**). From a perinatal statistics viewpoint, the term applies to in utero death of a fetus after 20 weeks' gestation before birth.

Antenatal demise occurs before labor. **Intrapartum demise** defines death that occurs after the onset of labor.

Significance

- Disseminated intravascular coagulation (DIC) is the most serious consequence, with prolonged fetal demise (>2 weeks) resulting from release of tissue thromboplastin from deteriorating fetal organs.
- Grief resolution may be prolonged if psychosocial issues are not appropriately addressed.

Fetal demise is most commonly idiopathic. When a cause is identified, risk factors include antiphospholipid syndrome, overt maternal diabetes, maternal trauma, severe maternal isoimmunization, fetal aneuploidy, and fetal infection.

Clinical Findings. Before 20 weeks' gestation, the most common finding is uterine **fundus smaller than dates**. After 20 weeks' gestation, the most common symptom is maternal report of **absence of fetal movements**.

Diagnosis. Ultrasound demonstration of lack of fetal cardiac activity.

Management varies:

- **DIC present.** DIC is usually not seen until 4 weeks after demise. Coagulopathy should be ruled out with appropriate laboratory testing: platelet count, d-dimer, fibrinogen, prothrombin time, partial thromboplastin time. If DIC is identified, immediate delivery is necessary with selective blood product transfusion as clinically indicated.
- **No DIC present.** Delivery may best be deferred for a number of days to allow for an appropriate grief response to begin. Or if the patient wishes conservative management, follow weekly serial DIC laboratory tests. 90% of patients start spontaneous labor after 2 weeks.
- **Mode of delivery.** A dilatation and evacuation (D&E) procedure may be appropriate in pregnancies of <23 weeks' gestation if no fetal autopsy is indicated. Induction of labor with vaginal prostaglandin is appropriate in pregnancies of ≥23 weeks or if a fetal autopsy is indicated. Cesarean delivery is almost never appropriate for dead fetus.
- **Psychosocial issues.** Acceptance of the reality of the loss may be enhanced by allowing the patient and her family to see the fetus, hold the fetus, name the fetus, and have a burial. Encouraging expression of feelings and tears may speed grief resolution.
- **Identify cause.** Workup may include cervical and placental cultures for suspected infection, **autopsy** for suspected lethal anatomic syndrome, **karyotype** for suspected aneuploidy, **total body x-ray** for suspected osteochondrodysplasia, maternal blood for **Kleihauer-Betke** (peripheral smear for suspected fetomaternal bleed). Amniocentesis can yield living fetal amniocyte cells although the fetus is demised. Up to 10% of the karyotypes show aneuploidy.

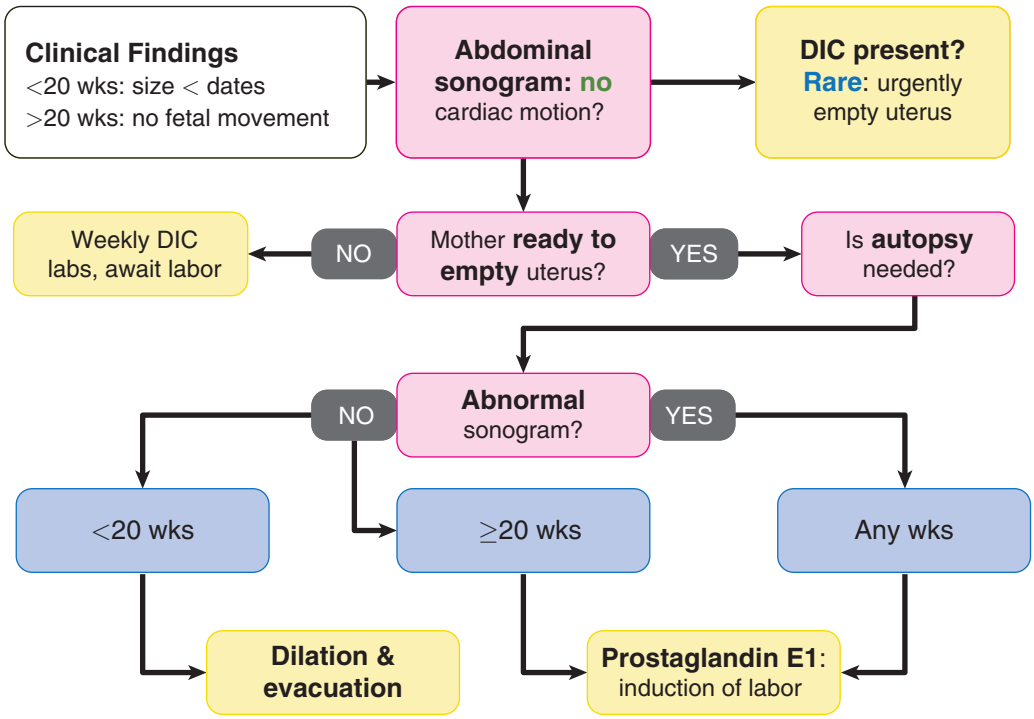

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Figure I-2-2. Approach to Fetal Demise

ECTOPIC PREGNANCY

A 28-year-old woman visits the emergency department complaining of unilateral left-sided abdominal pain and vaginal spotting of 3 days' duration. Her last menstrual period was 8 weeks ago, and before this episode she had menses every 28 days. Her only previous pregnancy was an uncomplicated term spontaneous vaginal delivery. She had used intrauterine contraception for 3 years in the past. On pelvic examination the uterus is slightly enlarged, and there is left adnexal tenderness but no palpable mass. Quantitative serum β-hCG value is 2,600 mIU.

OB Triad

Ectopic Pregnancy

- **Secondary** amenorrhea
- **Unilateral** abdominal/pelvic pain
- Vaginal bleeding

Ectopic pregnancy (1% of pregnancies; 15% if patient has had one ectopic pregnancy) is pregnancy in which implantation has occurred outside of the uterine cavity. The most common location is an oviduct; within the oviduct, the most common location is the distal ampulla.

With a positive pregnancy test, the **differential diagnosis** consists of a threatened abortion, incomplete abortion, ectopic pregnancy, and hydatidiform mole. In a reproductive-age woman with abnormal vaginal bleeding, always consider the possibility of pregnancy or complication of pregnancy.

The **most common** predisposing cause is previous pelvic inflammatory disease (PID). Ectopic pregnancy risk is increased from any obstruction of normal zygote migration to the uterine cavity from tubal scarring or adhesions from any origin: infectious (PID, IUD), postsurgical (tubal ligation, tubal surgery), or congenital (diethylstilbestrol [DES] exposure).

Table I-2-2. Risk Factors for Ectopic Pregnancy

Scarring or Adhesions Obstructing Normal Zygote Migration	
Infectious	Pelvic inflammatory disease
Postsurgical	Tuboplasty/ligation
Congenital	Diethylstilbestrol
Idiopathic	No risk factors

Clinical Findings.

- **Symptoms.** The **classic triad** with an unruptured ectopic pregnancy is amenorrhea, vaginal bleeding, and unilateral pelvic-abdominal pain. With a ruptured ectopic pregnancy, the symptoms will vary with the extent of intraperitoneal bleeding and irritation. Pain usually occurs after 6–8 menstrual weeks.
- **Signs.** The classic findings with an unruptured ectopic pregnancy are unilateral adnexal and cervical motion tenderness. Uterine enlargement and fever are usually absent. With a ruptured ectopic pregnancy, the findings reflect peritoneal irritation and the degree of hypovolemia. Hypotension and tachycardia indicate significant blood loss. This results in abdominal guarding and rigidity.
- **Investigative findings.** A β-hCG test will be positive. Sonography may or may not reveal an adnexal mass, but most significantly no intrauterine pregnancy (IUP) will be seen.

Diagnosis. The diagnosis of an unruptured ectopic pregnancy rests on the results of a quantitative serum β-hCG titer combined with the results of a vaginal sonogram. It is based on the assumption that when a normal intrauterine pregnancy has progressed to where it can be seen on vaginal sonogram at 5 weeks' gestation, the serum β-hCG titer will exceed 1,500 mIU. With the lower resolution of abdominal sonography, an IUP will not consistently be seen until 6 weeks' gestation. The β-hCG discriminatory threshold for an abdominal ultrasound to detect an intrauterine gestation is 6,500 mIU compared with 1,500 mIU for vaginal ultrasound.

Failure to see a normal intrauterine gestational sac when **β-hCG titer >1,500 mIU** is **presumptive diagnosis of an unruptured ectopic pregnancy**. No intrauterine pregnancy is seen with vaginal sonogram.

Note

Diagnosis of ectopic pregnancy is presumed when **β-hCG titer >1,500 mIU**.

Management.

- **Ruptured ectopic.** Diagnosis of a ruptured ectopic pregnancy is presumed with a history of amenorrhea, vaginal bleeding, and abdominal pain in the presence of a hemodynamically unstable patient. Immediate surgical intervention to stop the bleeding is vital, usually by laparotomy.
- **Intrauterine pregnancy.** If the sonogram reveals an IUP, management will be based on the findings. If the diagnosis is hydatidiform mole, the patient should be treated with a suction curettage and followed up on a weekly basis with β-hCG.
- **Possible ectopic.** If the sonogram does not reveal an IUP but the quantitative β-hCG is <1,500 mIU, it is impossible to differentiate a normal IUP from an ectopic pregnancy. Because β-hCG levels in a normal IUP double every 58 hours, the appropriate management will be to repeat the quantitative β-hCG and vaginal sonogram every 2–3 days until the β-hCG level exceeds 1,500 mIU. With that information an ectopic pregnancy can be distinguished from an IUP.

- **Unruptured ectopic.** Management can be medical with methotrexate or surgical with laparoscopy. Medical treatment is preferable because of the lower cost, with otherwise similar outcomes.
  - **Methotrexate.** This **folate antagonist** attacks rapidly proliferating tissues including trophoblastic villi. Criteria for methotrexate include pregnancy mass <3.5 cm diameter, absence of fetal heart motion, β-hCG level <6,000 mIU, and no history of folic supplementation. Single dose 1 mg/kg is 90% successful. Patients with an ectopic pregnancy should be advised of the somewhat increased incidence of recurrent ectopic pregnancies. Follow-up with **serial β-hCG levels** is crucial to ensure pregnancy resolution. Rh-negative women should be administered **RhoGAM**.
  - **Laparoscopy.** If criteria for methotrexate are not met, surgical evaluation is performed through a laparoscopy or through a laparotomy incision. The preferred procedure for an unruptured ampullary tubal pregnancy is a **salpingostomy**, in which the trophoblastic villi are dissected free preserving the oviduct. Isthmic tubal pregnancies are managed with a **segmental resection**, in which the tubal segment containing the pregnancy is resected.
  - **Salpingectomy** is reserved for the patient with a ruptured ectopic pregnancy or those with no desire for further fertility. After a salpingostomy, β-hCG titers should be obtained on a weekly basis to make sure there is resolution of the pregnancy. Rh-negative women should be administered **RhoGAM**.

Patients who are treated with methotrexate or salpingostomy should be followed up with β-hCG titers to ensure there has been complete destruction of the ectopic trophoblastic villi.

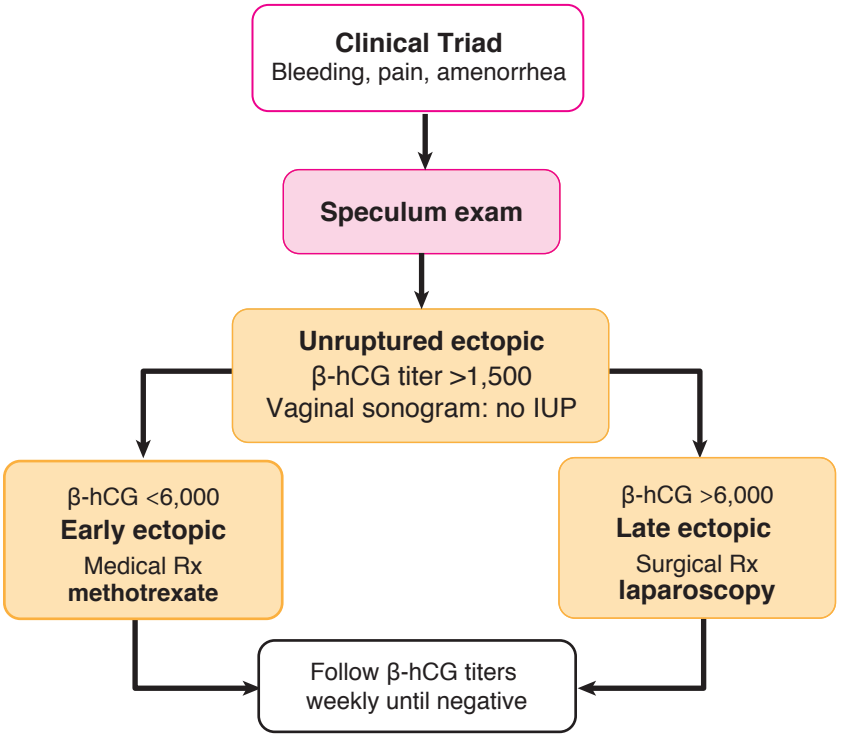

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Figure I-2-3. Approach to Ectopic Pregnancy

Obstetric Procedures 3

Learning Objectives

- ❑ Describe routine and high-risk prenatal diagnostic testing
- ❑ Describe the appropriate use of obstetrical monitoring procedures including U/S, chorionic villus sampling, amniocentesis, percutaneous umbilical blood sampling, and fetoscopy

OBSTETRICAL ULTRASOUND

Obstetrical ultrasound uses low-energy, high-frequency sound waves.

- Early first-trimester ultrasound utilizes a crown–rump **(CRL)** measurement.
- Later second- and third-trimester ultrasound utilizes four measurements: biparietal diameter **(BPD)**, head circumference **(HC)**, abdominal circumference **(AC)**, and femur length **(FL)**.

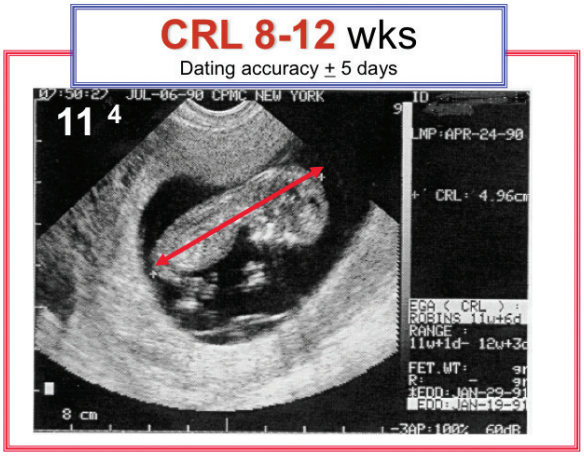

Figure I-3-1. First-Trimester Obstetrical U/S Showing Crown Rump Length

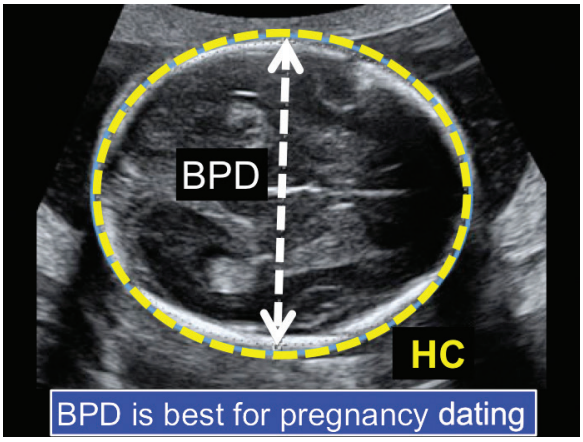

Figure I-3-2. Second- and Third-Trimester Obstetrical U/S Showing Biparietal Diameter and Head Circumference

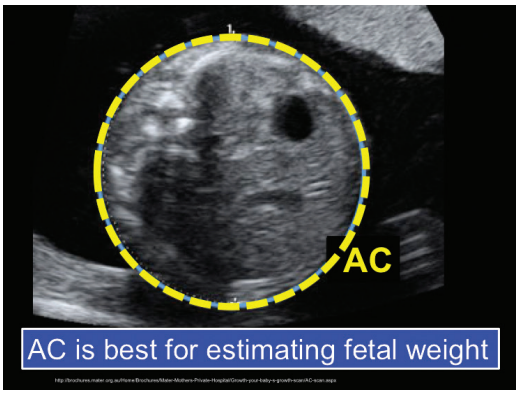

Figure I-3-3. Second- and Third-Trimester Obstetrical U/S Showing Abdominal Circumference

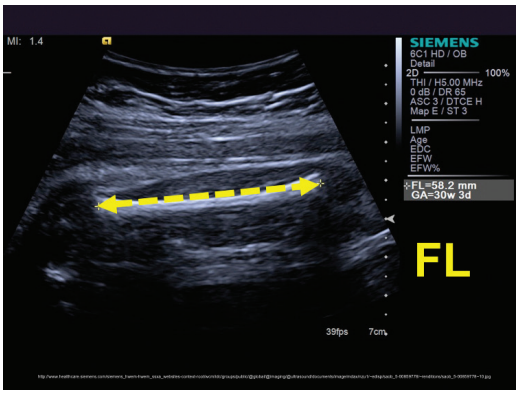

Figure I-3-4. Second- and Third-Trimester Obstetrical U/S Showing Femur Length

Modalities

High-Yield

- **Transvaginal sonogram** is used in first trimester, producing high-resolution images that are not influenced by maternal BMI. Dating accuracy of early first-trimester sonogram is +/— 5–7 days.
- **Transabdominal sonogram** is used any time during the pregnancy, but image quality may be limited by maternal obesity. No adverse fetal effects have been noted during decades of research studies. Dating accuracy of early second trimester sonogram is +/— 7–10 days.
- **Doppler** ultrasound study is used to assess umbilical artery (UA) and middle cerebral artery (MCA) blood flow. This modality assesses fetal well-being in **IUGR** pregnancies, as well as fetal anemia in alloimmunized pregnancies.

Indications

There are many reasons to use obstetrical ultrasound.

- Pregnancy location & viability, gestational age dating
- Multiple gestation (zygosity, chorionicity, amnionicity)
- Amniotic fluid volume (oligohydramnios, polyhydramnios)
- Fetal growth (IUGR, macrosomia)
- Fetal anomalies, fetal well-being
- Pregnancy bleeding, fetal anemia

Genetic Sonogram

High-Yield

Genetic sonogram, ideally performed at 18–20 weeks, looks for anatomic markers of fetal aneuploidy which include:

- **Generic:** any structural abnormalities
- **Specific:** nuchal skin fold thickness (strongest predictor), short long bones, pyelectasis, echogenic intracardiac focus, hyperechoic bowel.

Note

Accuracy of Sonogram Dating

Crown-Rump Length (CRL)

+/— 5 days	<9 weeks
+/— 7 days	9–14 weeks

BPD, HC, AC, FL

+/— 7 days	14–16 weeks
+/— 10 days	16–22 weeks
+/— 14 days	22–28 weeks
+/— 21 days	28+ weeks

Nuchal Translucency

High-Yield

Nuchal translucency (NT) measurement is a screening test performed with sonogram between 10–14 weeks, measuring the fetal fluid collection behind the neck.

- A thickened NT increases the likelihood of aneuploidy and cardiac disease.
- It is combined with two maternal blood tests (free β-hCG & PAPP-A) in first-trimester screening to increase the sensitivity and specificity for aneuploidy screening.

INVASIVE PROCEDURES

Chorionic Villus Sampling

High-Yield

Chorionic villus sampling (CVS) is a diagnostic outpatient office procedure performed under ultrasound (U/S) guidance without anesthesia. Pregnancy loss rate is 0.7%.

- The catheter is placed directly into the placental tissue without entering the amniotic cavity. Chorionic villi, which are placental precursors, are aspirated from a pregnant uterus between 10 and 12 weeks' gestation.
- The tissue is sent to the laboratory for karyotyping. The chromosomes of the villi are almost always identical to those of the embryo.
- The procedure can be performed either **transcervically** or **transabdominally**. Since the fetus and chorionic villi are both derived from a common origin (the zygote), their karyotype is identical more than 99% of the time.

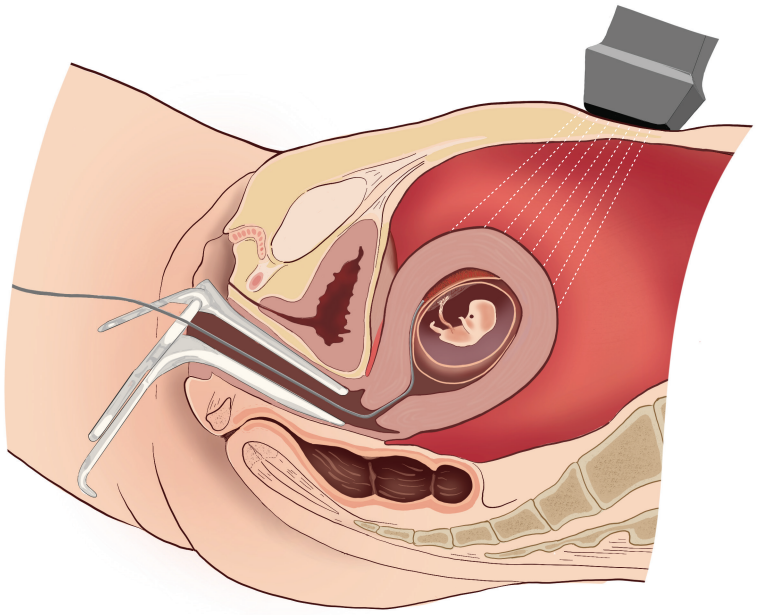

Figure I-3-5. Chorionic Villus Sampling

Amniocentesis

High-Yield

Amniocentesis is a diagnostic, outpatient office procedure performed **after 15 weeks** under U/S guidance without anesthesia. Pregnancy loss rate is 0.5%

- A needle is placed into a pocket of amniotic fluid under direct U/S guidance, aspirating amniotic fluid containing desquamated living fetal cells (**amniocytes**).
- Fetal karyotyping is performed on amniocytes. NTD (neural tube defect) screening is performed on amniotic fluid with biochemical analysis **(AFP and acetylcholinesterase)**.

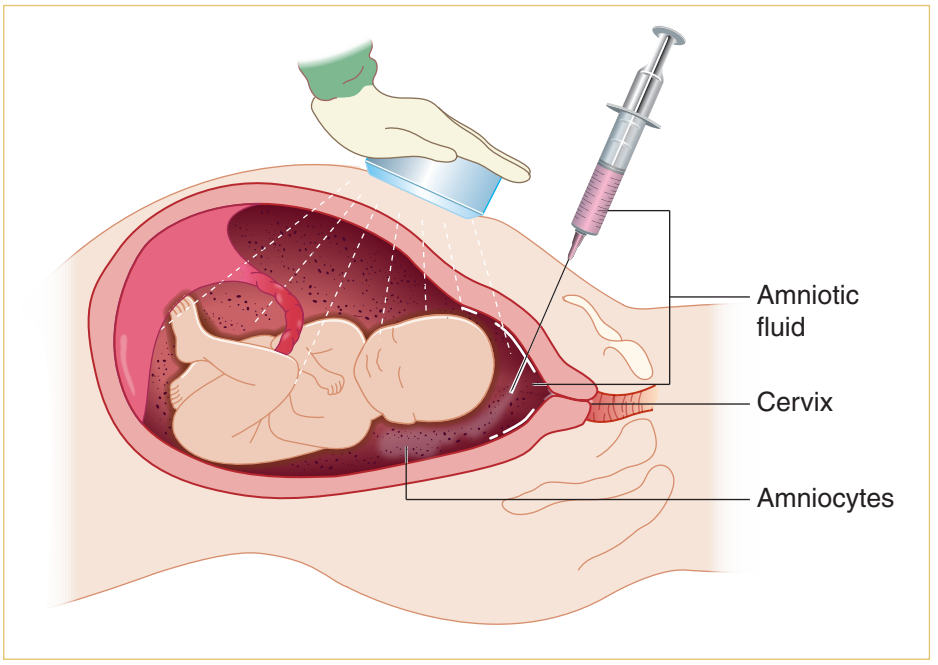

Figure I-3-6. Amniocentesis

Percutaneous Umbilical Blood Sample (PUBS)

High-Yield

This transabdominal procedure, performed under U/S guidance, aspirates fetal blood from the umbilical vein after 20 weeks' gestation. It can be **diagnostic** (e.g., blood gases, karyotype, IgG and IgM antibodies) or **therapeutic** (e.g., intrauterine transfusion for fetal anemia). Pregnancy loss rate is **1–2%**.

Fetoscopy

High-Yield

A fetoscopy is a **transabdominal** procedure performed with a fiberoptic scope in the operating room **after 20 weeks** under regional or general anesthesia. Indications for fetoscopy include **intrauterine surgery** or **fetal skin biopsy**.

Laser is used for coagulating placental vessels in twin–twin transfusion syndrome (TTTS). Skin biopsy may be performed for suspected fetal ichthyosis. **Risks** are bleeding, infection, membrane rupture, fetal loss. Pregnancy loss rate is **2–5%**.

PRENATAL DIAGNOSTIC TESTING

Table I-3-1. Prenatal Diagnostic Testing

CVS	10–12 wks	0.7% pregnancy loss rate
		Placental precursor
Nuchal Translucency	10–14 wks	0% pregnancy loss rate
		Nuchal T, PAPP-A, free β-hCG
Cell-free DNA	>10 wks	0% pregnancy loss rate
		Maternal blood with cell-free fetal/placental DNA
Amniocentesis	≥15 wks	0.5% pregnancy loss rate
		Amniocytes; amniotic fluid AFP
Expanded X-AFP	15–20 wks	0% pregnancy loss rate
		MS-AFP, β-hCG, estriol, inhibin
Sonogram	18–20 wks	0% pregnancy loss rate
		Noninvasive anatomy scan
Fetoscopy	18–20 wks	3–5% pregnancy loss rate
		Laser in TTTS, fetal biopsy
PUBS	≥20 wks	1–2% pregnancy loss rate
		Umbilical vein blood

Cell-Free DNA

This is a noninvasive screening procedure in which a maternal blood sample is drawn after 9 weeks' gestation.

- The test measures small fragments of fetal/placental DNA in maternal blood to determine the risk of fetal aneuploidy.
- If the results indicate an increased risk of abnormalities, a definitive test should be performed, such as chorionic villus sampling or amniocentesis.

Prenatal Management of the Normal Pregnancy

4

Learning Objectives

- ❏ Describe how to diagnose pregnancy, establish gestational age, and identify risk factors
- ❏ List normal pregnancy events and complaints
- ❏ Differentiate between safe and unsafe immunizations in pregnancy

DIAGNOSING PREGNANCY

Presumptive signs of pregnancy include amenorrhea, breast tenderness, nausea and vomiting, increased skin pigmentation, and skin striae.

Probable signs of pregnancy include **enlargement of the uterus**, maternal sensation of uterine contractions or fetal movement, Hegar's sign (softening of the junction between the corpus and cervix), and positive urine or **serum β-human chorionic gonadotropin** (**β-hCG**) testing.

Positive signs of pregnancy include hearing **fetal heart tones**, **sonographic visualization of a fetus**, perception of fetal movements by an external examiner, and x-ray showing a fetal skeleton.

Table I-4-1. Signs of Pregnancy

Presumptive	Unrelated to uterus or fetus	Amenorrhea
Probable	Related to uterus or mother's feelings	Increased uterine size β-hCG
Definitive	Related to the fetus	Sonogram of fetus Heard FHT

ESTABLISHING GESTATIONAL AGE

Establishing gestational age is one of the most important purposes of the first prenatal visit. The **earlier the gestational age, the more accurate the dating**.

- **Conception dating:** Normal pregnancy duration postconception is 266 days or 38 weeks. However, most women cannot accurately identify conception date.
- **Menstrual dating:** Because the last menstrual period (LMP) is more easily identified than conception, pregnancy duration in most cases is determined to be 280 days or 40 weeks from the LMP. We assume a 28-day menstrual cycle in which ovulation occurs on day 14 after the beginning of the LMP. Yet only 10% of women have a 28-day cycle. A normal cycle length can vary from 21–35 days.

- **Ultrasound dating:** The accuracy of ultrasound dating is gestational-age-dependent. Earlier sonograms are more accurate than later ones.
  - If the difference between menstrual dates and ultrasound dates is **within the normal range** of variation, use the **menstrual dates**.
  - If the difference between menstrual dates and ultrasound dates **is outside the normal range** of variation, use the **ultrasound dates**.
- **Naegele's rule:** Assuming 28-day cycles, a due date can be estimated as the LMP minus 3 months + 7 days.

Table I-4-2. Pregnancy Dating

Duration of pregnancy using:	Conceptional dating	266 days or 38 weeks
Duration of pregnancy using:	Menstrual dating	280 days or 40 weeks
Assumed cycle length		28 days
Calculate due date	Naegele's rule	Last menstrual period—3 months + 7 days

- **Basal body temperature chart:** The rise in basal body temperature (BBT) is assumed to be caused by the thermogenic effect of progesterone produced by the corpus luteum that formed after ovulation. The accuracy of BBT is ±1 week.
- **Menstrual history:** Menstrual dating assumes ovulation occurred on day 14 after the first day of the LMP. However, normal menstrual cycles can vary from 21 to 35 days, making ovulation possible on day 7 to day 21. Because most women's cycles are more or less than 28 days, adjustment of the due date may be necessary. Accuracy of menstrual dating is variable depending on the patient's memory and record keeping. The accuracy of menstrual history is ±1 week.

OB Triad

Precise Day of Ovulation

- 21-day cycle: day 7
- 28-day cycle: day 14
- 35-day cycle: day 21

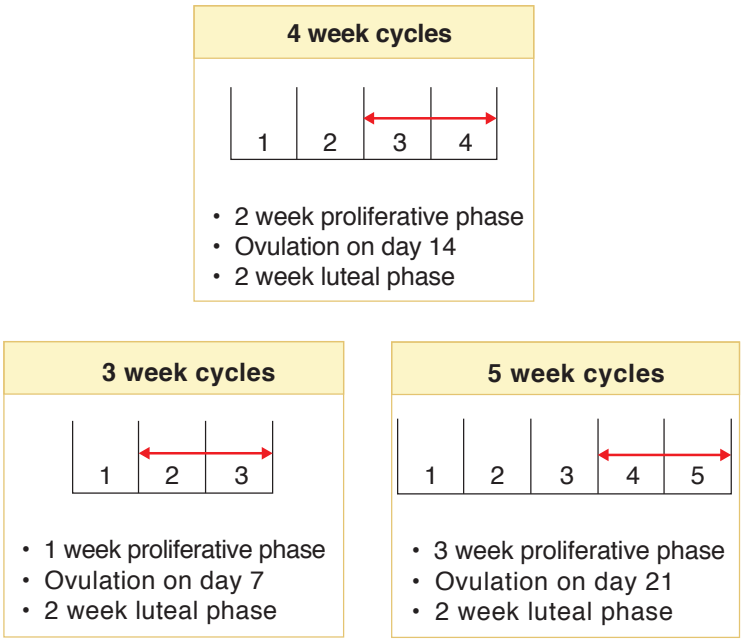

Figure I-4-1. Variations in Menstrual Cycle

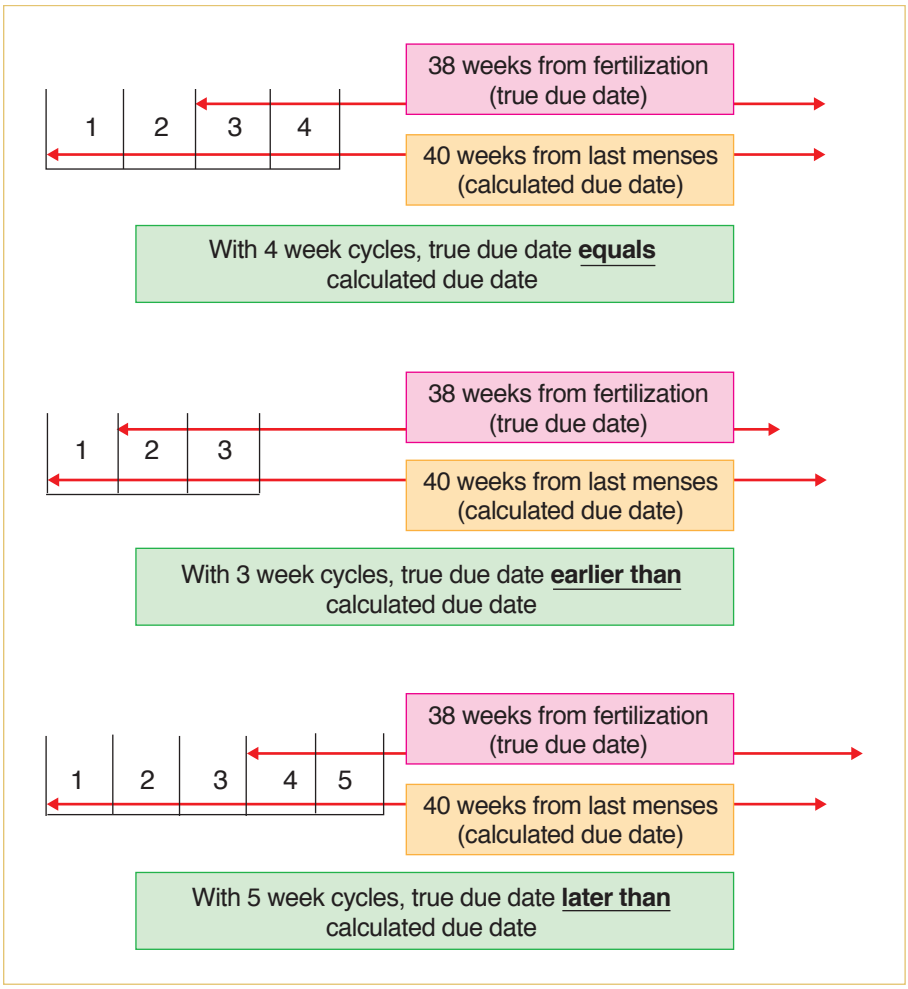

Figure I-4-2. Effect of Cycle Length on Calculated Due Date

IDENTIFYING PRENATAL RISK FACTORS

Obstetrical history: number of pregnancies, pregnancy duration, complications, mode of delivery, perinatal outcome

Medical and surgical history: diabetes mellitus, hypertension, cardiac, thyroid, seizure disorder, anemia

Social history: educational level, marital status, social support, abusive relationships

Family history: inherited diseases, intellectual disability birth defects, perinatal deaths

Sexual history: age of first intercourse, current partners, lifetime sexual partners, previous sexual abuse

Lifestyle: alcohol, tobacco, recreational drugs, poor nutrition, eating disorders

Teratogenic exposure: x-radiation, toxins, chemicals, prescription medications

NORMAL PREGNANCY EVENTS

First Trimester

Assuming a 40-menstrual-week pregnancy, the first trimester is assumed to extend from conception through to 13 weeks.

- Normal symptoms seen in the majority of pregnancies include nausea, vomiting, fatigue, breast tenderness, and frequent urination.
- **Spotting and bleeding** occur in 20% of pregnancies, 50% of which will continue successfully.
- Average weight gain is 5–8 pounds.
- Complications include spontaneous abortion.

Second Trimester

Assuming a 40-menstrual-week pregnancy, the second trimester is assumed to extend from 13–26 weeks.

- Normal symptoms are an improved feeling of general well-being.
- Round ligament pain is common.
- **Braxton-Hicks** contractions are painless, low-intensity, long-duration contractions that can be palpated as early as 14 weeks.
- **Quickening** (maternal awareness of fetal movement) is detected at 18–20 weeks by primigravidas and 16–20 weeks by multigravidas.
- Average weight gain is 1 pound per week after 20 weeks.
- Complications include incompetent cervix (painless cervical dilation leading to delivery of a nonviable fetus), premature membrane rupture, and premature labor.

Third Trimester

Assuming a 40-menstrual-week pregnancy, the third trimester is assumed to extend from 26–40 weeks.

- Normal symptoms include decreased libido, lower back and leg pain, urinary frequency, and Braxton-Hicks contractions.
- **Lightening** describes descent of the fetal head into the pelvis resulting in easier maternal breathing, pelvic pressure.
- **Bloody show** describes vaginal passage of bloody endocervical mucus, the result of cervical dilation before labor.
- Average weight gain is 1 pound per week after 20 weeks.
- Complications include premature membrane rupture, premature labor, preeclampsia, urinary tract infection, anemia, and gestational diabetes.

NORMAL PREGNANCY COMPLAINTS

- **Backache** is very common, especially in the latter part of pregnancy because of the change in center of gravity with the enlarging uterus. Muscles and ligaments are now used that otherwise would not be. **Management** is encouragement of correct posture.
- **Bleeding gums** are caused by the increase of blood flow to the gums with pregnancy. If it is associated with clinical swelling, it is known as epulis. **Management** is conservative.
- **Breast enlargement:** Each breast increases in size by 400 grams and may result in an increase of 1–2 cup sizes. **Management** is a support bra.
- **Carpal tunnel:** As many as 50% of pregnant women will experience numbness, tingling, burning, or pain in at least 2 of the 3 digits supplied by the median nerve. **Management** is fitting with a wrist splint (most cases will spontaneously resolve after delivery).
- **Complexion changes:** Some women develop brownish or yellowish patches called chloasma, or the "mask of pregnancy," on their faces. Others may develop a linea nigra on the lower abdominal midline, as well as hyperpigmentation of the nipples and external genitalia. **Management** is conservative.
- **Dizziness:** BP normally decreases in pregnancy, which may lead to postural hypotension. **Management** is avoiding rapid postural changes, such as standing up quickly.
- **Fatigue** is very common in pregnancy, probably because of rapid hormonal changes. **Management** is adequate rest and avoiding excessive activity.
- **Fluid retention:** Increased circulating steroid levels and decreased serum albumin results in edema in over half of pregnant women. Edema is not a criterion for pre-eclampsia. **Management** is elevating legs and using support hose.
- **Hair and nails:** Hair shedding decreases in pregnancy. **Telogen effluvium** is the excessive shedding of hair occurring 1–5 months after pregnancy. Telogen effluvium occurs in 40–50% of women. Nails may become more brittle. **Management** is conservative.
- **Headaches:** Muscle contraction and migraine headaches are more common in pregnancy, probably because of increased estrogen levels. **Management** is physical therapy (e.g., ice packs, massage) with medication only as a last resort.
- **Leg cramps:** Lower extremity muscle cramps are frequent in pregnancy. **Management** is hydration, stretching exercises, and calcium supplementation.
- **Morning sickness:** Nausea and vomiting are common in early pregnancy and are probably mediated by elevated hCG levels. **Management** is eating small meals (with emphasis on crackers and carbohydrates).
- **Nosebleeds:** Vasodilation and increased vascular supply results in more frequent nosebleeds. **Management** is saline drops and the avoidance of nasal sprays.
- **Stretch marks:** Genetic predisposition and pregnancy can result in striae gravidarum. Women with stretch marks have increased risk of delivery lacerations. **Management** is conservative.
- **Stress incontinence:** Pressure on the bladder with an enlarging uterus frequently results in an involuntary loss of urine. **Management** is strengthening the pelvic diaphragm with Kegel exercises.
- **Varicose veins:** Increased blood volume, the relaxing effect of progesterone on smooth muscle, and an increased lower-extremity venous pressure often result in lower-extremity varicosities. **Management** is discouraging prolonged standing and sitting.

Table I-4-3. Pregnancy Danger Signs

Complaint	Possible Diagnosis
Vaginal bleeding	Early (spontaneous abortion) Later (abruption, previa)
Vaginal fluid leakage	Rupture of membrane (ROM) Urinary incontinence
Epigastric pain	Severe preeclampsia
Uterine cramping	Preterm labor Preterm contractions
↓ Fetal movement	Fetal compromise
Persistent vomiting	Hyperemesis (early) Hepatitis Pyelonephritis
Headache, visual changes	Severe preeclampsia
Pain with urination	Cystitis Pyelonephritis
Chills and fever	Pyelonephritis Chorioamnionitis

IMMUNIZATIONS

Safe Immunizations

High-Yield

Safe immunizations include antigens from killed or inactivated organisms:

- Influenza (all pregnant women in flu season)
- Tetanus, diphtheria, pertussis (**Tdap**) (**all pregnant women** irrespective of their prior history); to maximize the maternal antibody response and passive antibody transfer to the infant, optimal timing is between 27–36 weeks gestation. For women not previously vaccinated, if Tdap is not administered during pregnancy it should be administered immediately postpartum.
- Hepatitis B (pre- and postexposure)
- Hepatitis A (pre- and postexposure)
- Pneumococcus (only high-risk women)
- Meningococcus (in unusual outbreaks)
- Typhoid (not routinely recommended)

Unsafe Immunizations

High-Yield

Unsafe immunizations include antigens from live attenuated organisms:

- MMR (measles, mumps, rubella)
- Polio
- Yellow fever
- Varicella

Prenatal Laboratory Testing 5

Learning Objectives

- ❑ Clarify the difference between laboratory tests in the first, second, and third trimesters
- ❑ Explain the importance and function of each laboratory test

FIRST TRIMESTER LABORATORY TESTS

A 21-year-old primigravida G1 PO presents for her first prenatal visit at 11 weeks' gestation, which is confirmed by obstetric sonogram. She has no risk factors. What laboratory tests should be ordered on her?

Complete Blood Count (CBC)

High-Yield

- **Hemoglobin and hematocrit** (normal pregnancy hemoglobin 10–12 g/dL): Although nonpregnancy female hemoglobin reference range is 12–14 g/dL, normal values in pregnancy will reflect the dilutional effect of greater plasma volume increase than red blood cell (RBC) mass.
- **Mean corpuscular volume (MCV):** Because hemoglobin and hematocrit reflect pregnancy dilution, MCV may be the most reliable predictor of true anemia. A low hemoglobin and low MCV (<80 μm^3) most commonly suggests iron deficiency, but may also be caused by thalassemia. A low hemoglobin and high MCV (>100) suggests folate deficiency or, rarely, vitamin B12 deficiency.
- **Platelet count:** A low platelet count (<150,000/mm^3) is most likely indicative of gestational (pregnancy-induced) thrombocytopenia. Preeclampsia with severe features and idiopathic thrombocytopenic purpura (ITP) are uncommon causes of low platelets. Disseminated intravascular coagulation is rare.
- **Leukocyte count** (normal pregnancy white blood cell count in pregnancy is up to 16,000/mm^3): Leukopenia suggests immune suppression or leukemia.

Rubella IgG Antibody

High-Yield

- **Immunity:** The presence of rubella antibodies rules out a primary infection during the pregnancy. Antibodies derived from a natural, wild infection lead to lifelong immunity. Antibodies from a live-attenuated virus are not as durable.
- **Susceptibility:** An absence of antibodies leaves the woman at risk for a primary rubella infection in pregnancy that can have devastating fetal effects, particularly in the first trimester. Rubella immunization is contraindicated in pregnancy because it is made from a live virus but is recommended after delivery.

Hepatitis B Virus (HBV)

High-Yield

- HBV **surface antibodies** are expected from a successful vaccination.
- The presence of HBV **surface antigen** represents either a previous or current infection. HBV surface antigen indicates **high risk for vertical transmission** of HBV from the mother to the fetus or neonate. This is the only specific hepatitis test obtained routinely on the prenatal laboratory panel.
- The presence of HBV **E antigen** signifies a highly infectious state.

Type, Rh, and Antibody Screening

High-Yield

- The patient's blood type and Rh is determined with the **direct Coombs test**. If the patient is Rh-negative, she is at risk for anti-D isoimmunization.
- The presence of atypical RBC antibodies is determined with the **indirect Coombs test** (or atypical antibody test [AAT]). Isoimmunization is identified if atypical antibodies are present. Follow-up testing is necessary to identify whether the fetus is at risk.

STD Screening

High-Yield

- **Cervical cultures:** Screening cultures for **chlamydia** and **gonorrhea** will identify whether the fetus is at risk from delivery through an infected birth canal.
- **Syphilis:** Nonspecific screening tests (**venereal disease research laboratory** [VDRL] or **rapid plasma reagin** [RPR]) are performed on all pregnant women. Positive screening tests must be followed up with treponema-specific tests (microhemagglutination assay for antibodies to *T. pallidum* [**MHA-TP**] or **fluorescent treponema antibody absorption** [FTA]). **Treatment** of syphilis in pregnancy requires penicillin to ensure adequate fetal treatment.
- **Hepatitis B:** Maternal hepatitis B surface antigen (HBsAg) screening assesses if the mother could have active hepatitis, as well as if she could transmit HBV to her newborn at the time of delivery.

Table I-5-1. Initial Prenatal Labs for STDs

Chlamydia/Gonorrhea (GC)	Screening	DNA probes
Hepatitis B virus	Screening	Hepatitis B surface antigen (HBsAg)
Syphilis	Screening	VDRL/rapid plasma reagin (RPR)
	Definitive	Microhemagglutination assay/fluorescent treponema antibody absorption (MHA/FTA)
HIV	Screening	Enzyme-linked, immunosorbent assay (ELISA)
	Definitive	Western Blot

Urine Screening

High-Yield

- **Urinalysis:** Assessment of proteinuria, ketones, glucose, leukocytes, and bacteria is important to screen for **underlying renal disease**, diabetes, and infection.
- **Culture:** Screening for **asymptomatic bacteriuria** (ASB) is essential (~8% of pregnant women have ASB). Left untreated, 30% of ASB progresses to pyelonephritis, which is associated with septic shock, pulmonary edema, and adult respiratory distress syndrome.

Tuberculosis (TB) Screening

High-Yield

Antituberculosis drugs are not contraindicated in pregnancy.

- **PPD or tine test:** This screening skin test determines **previous exposure to TB**. TB screening is not done routinely and performed only on high-risk populations. A negative test means no further follow-up is necessary. A positive test is induration, not erythema.
- **Chest x-ray:** If the screening skin test is positive, a chest x-ray is performed to rule out active disease. If the chest x-ray is **negative**, isoniazid (INH) (and vitamin B6) is given for 9 months. If the chest x-ray is **positive**, induced sputum is cultured and triple medications begun until cultures define the organisms involved.

HIV Screening

High-Yield

HIV screening is recommended for all pregnant women as part of the initial lab testing. The CDC recommends **Informed Refusal** (or "**Opt Out**," where a patient is tested unless she refuses), rather than **Informed Consent** (or "**Opt In**," where a patient must specifically consent). Retesting should take place in the third trimester in areas of high HIV prevalence or an at-risk patient. Rapid HIV testing in labor is recommended if the patient's HIV status is not known.

- The **ELISA** test (**screening test**) assesses presence of detectable HIV antibodies. A three-month lag exists between HIV infection and a positive ELISA test. All babies born to HIV-positive women will be HIV-antibody positive from passive maternal antibodies.
- The **Western blot** test (**definitive test**) identifies the presence of HIV core and envelope antigens. Triple antiviral therapy is recommended for all HIV-positive women starting at 14 weeks and continuing through delivery. With cesarean delivery and triple antiviral therapy, transmission rates are as low as 1%.

SECOND TRIMESTER LABORATORY TESTS

A 23-year-old woman (G3 P1 Ab1) is seen at 16 weeks' gestation. Her previous pregnancy resulted in an anencephalic fetus that did not survive. She took 4 mg of folate preconception before this pregnancy but wants to know whether this fetus is affected.

Maternal Serum α-Fetoprotein (MS-AFP)

High-Yield

- **Alpha-fetoprotein (AFP)** is the **major serum glycoprotein** of the embryo. The concentration peaks at 12 weeks in the fetus and amniotic fluid (AF), then rises until 30 weeks in the maternal serum. Fetal structural defects (open neural tube defect

[NTD] and ventral wall defects) result in increased spillage into the amniotic fluid and maternal serum. Other causes include twin pregnancy, placental bleeding, fetal renal disease, and sacrococcygeal teratoma.

Major Serum Glycoprotein of the Embryo		
Normal AFP changes	Fetal serum	Peaks at **12** weeks
	Amniotic fluid	Peaks at **12** weeks
	Maternal serum	Peaks at **30** weeks

- **MS-AFP** is reported in multiples of the median (MoM) and is always performed as part of multiple marker screenings. Maternal serum testing is performed within a gestational window of **15–20 weeks**. Because reference ranges are specific to gestational age, accurate pregnancy dating is imperative.

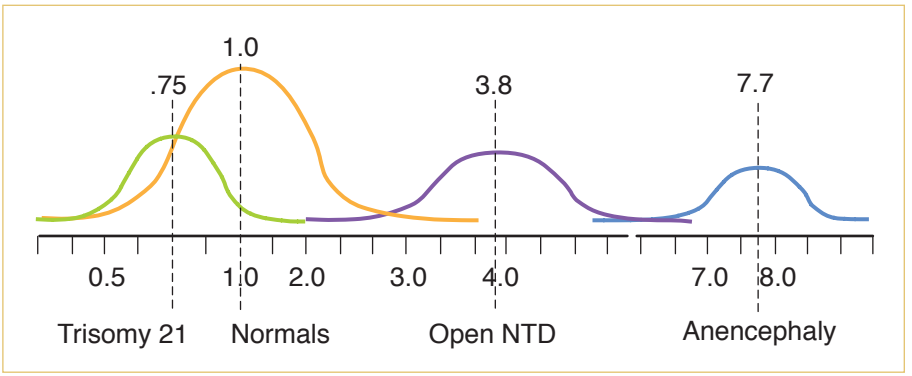

Figure I-5-1. Midpoints of MSAFP

Elevated MS-AFP: A positive high value is >2.5 MoM. The next step in management is to obtain an obstetric ultrasound to confirm gestational dating. The most common cause of an elevated MS-AFP is **dating error.**

- If the true gestational age is more advanced than the assumed gestational age, it would explain the positive high value. In cases of dating error, repeat the MS-AFP if the pregnancy is still within the 15- to 20-week window. A normal MS-AFP will be reassuring.
- If the dates are correct and no explanation is seen on sonogram, perform amniocentesis for AF-AFP determination and acetylcholinesterase activity. Elevated levels of **AF acetylcholinesterase** activity are specific to open NTD.
- With unexplained elevated MS-AFP but normal AF-AFP, the pregnancy is statistically at risk for intrauterine growth restriction (IUGR), stillbirth, and preeclampsia.

Low MS-AFP: A positive low value is **<0.50 MoM**. The sensitivity of MS-AFP alone for trisomy 21 is only 20%. The next step in management is to obtain an obstetric ultrasound to confirm gestational dating. The most common cause of a low MS-AFP is **dating error**.

- If the true gestational age is less than the assumed gestational age, it would explain the positive low value. In cases of dating error, repeat the MS-AFP if the pregnancy is still within the window. A normal MS-AFP will be reassuring.
- If the dates are correct and no explanation is seen on sonogram, perform amniocentesis for **karyotype**.

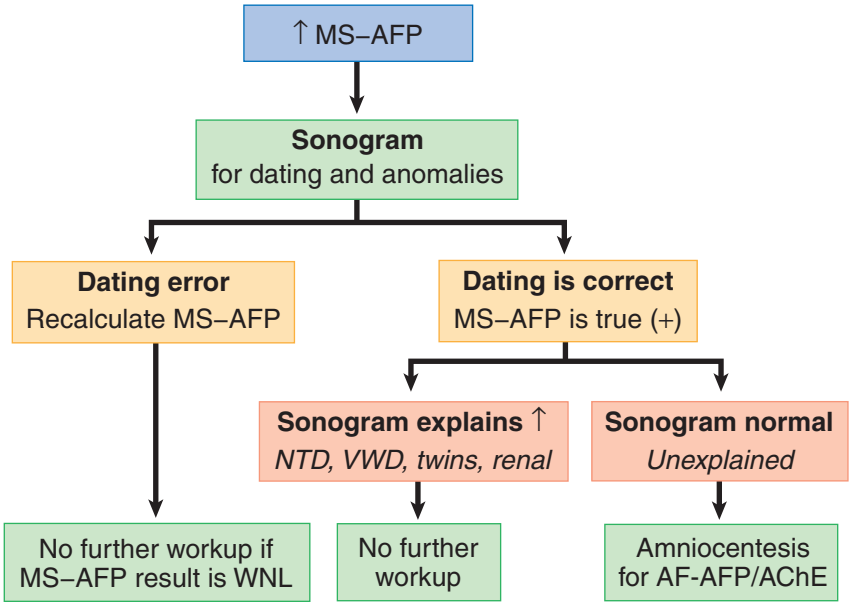

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Figure I-5-2. Follow-up of High MS-AFP

Quadruple Marker Screen

High-Yield

- **Trisomy screening:** The sensitivity for trisomy 21 detection can be increased to 80% by performing maternal serum screen for not only **MS-AFP**, but also **hCG**, **estriol**, and **inhibin-A**. The window for testing is also **15–20 weeks**. Because reference values are gestational age specific, accurate dating is important.
- **Trisomy 21:** With Down syndrome, levels for MS-AFP and estriol are decreased, but **hCG and inhibin-A are increased**. Perform an amniocentesis for **karyotype.**
- **Trisomy 18:** With Edward syndrome, levels for **all four markers** (MS-AFP, estriol, inhibin-A, and hCG) **are decreased**. Perform an amniocentesis for **karyotype.**

THIRD-TRIMESTER LABORATORY TESTS

A 33-year-old woman (G4 P3) is at 25 weeks' gestation. Her height is 63 inches (160 cm) and weight 250 pounds (113 kg) for a BMI of 44.3. She has gained 30 pounds thus far this pregnancy. With her last pregnancy she gained 60 pounds, was diagnosed with gestational diabetes, and delivered a 4,300-g female neonate by cesarean section. She wants to know whether she has diabetes with this pregnancy.

Diabetic Testing

- **1-h 50-g oral glucose tolerance test** (OGTT): **screening** test administered to all pregnant women between 24–28 weeks' gestation (no fasting state is needed). A 50-g glucose load is given, and serum glucose is measured 1 h later. A **normal value** is <140 mg/dL. An abnormal value is ≥140 mg/dL (15% of pregnant women). **Management** is a 3-h 100-g OGTT.

Note

For more information on diabetic testing and anemia, see Obstetric Complications.

- **3-h 100-g OGTT: definitive** test for glucose intolerance in pregnancy (15% of women with an abnormal screening test will be found to have gestational diabetes mellitus). After an overnight fast, a fasting blood sugar (FBS) is drawn. An FBS value >125 mg/dL indicates overt diabetes mellitus, and no further testing is performed. An FBS value <126 mg/dL requires administration of a 100-g glucose load, followed by glucose levels at 1, 2, and 3 h.
  - **Normal values** are FBS <95 mg/dL, 1 h <180 mg/dL, 2 h <155 mg/dL, and 3 h <140 mg/dL.
  - Gestational diabetes is diagnosed if ≥2 values are abnormal.
  - Impaired glucose intolerance is diagnosed if only 1 value is abnormal.

Complete Blood Count

- **Anemia:** A complete blood count (CBC) should be performed between 24–28 weeks' gestation in all women. With the increasing diversion of iron to the fetus in the second and third trimester, iron deficiency, which was not present early in pregnancy, may develop (particularly in those not taking iron supplementation).
  - Hemoglobin <10 g/dL is considered anemia.
  - The most common cause is **iron deficiency**, which occurs only after bone marrow iron stores are completely depleted.
- **Platelet count:** Reassessment of pregnancy-induced thrombocytopenia can be also be done with the CBC.

Atypical Antibody Screen

- Before giving prophylactic RhoGAM to an Rh-negative woman, an indirect Coombs test is performed at 28 weeks. This is obtained to ensure she has not become isoimmunized since her previous negative AAT earlier in pregnancy.
- Two-tenths of a percent of Rh-negative women will become isoimmunized from spontaneous feto-maternal bleeding before 28 weeks.
- If it is discovered that the patient already has anti-D antibodies, administration of RhoGAM is futile.

Late Pregnancy Bleeding 6

Learning Objectives

- ❑ Differentiate between placental disorders and late pregnancy bleeding, including abruptio placentae, placenta previa, vasa previa, placenta accreta, placenta increta, and placenta percreta
- ❑ Describe the risk factors for and prognosis of uterine rupture

LATE PREGNANCY BLEEDING

Late pregnancy bleeding is vaginal bleeding that occurs after 20 weeks' gestation. Prevalence is <5%, but when it does occur, prematurity and perinatal mortality quadruple.

- **Cervical** causes include erosion, polyps, and, rarely, carcinoma.
- **Vaginal** causes include varicosities and lacerations.
- **Placental** causes include abruptio placentae, placenta previa, and vasa previa.

Initial Evaluation. What are patient's vital signs? Are fetal heart tones present? What is fetal status? What is the nature and duration of the bleeding? Is there pain or contractions? What is the location of placental implantation?

Initial Investigation. Complete blood count, disseminated intravascular coagulation (DIC) workup (platelets, prothrombin time, partial thromboplastin time, fibrinogen, **D-dimer**), type and cross-match, and sonogram for placental location. **Never perform a digital or speculum examination until ultrasound study rules out placenta previa.**

Initial Management. Start an IV line with a large-bore needle; if maternal vital signs are unstable, run isotonic fluids without dextrose wide open and place a urinary catheter to monitor urine output. If fetal jeopardy is present or gestational age is ±36 weeks, the goal is delivery.

Common Causes

High-Yield

Abruptio placentae

A 32-year-old multigravida at 31 weeks' gestation is admitted to the birthing unit after a motor-vehicle accident. She complains of sudden onset of moderate vaginal bleeding for the past hour. She has intense, constant uterine pain and frequent contractions. Fetal heart tones are regular at 145 beats/min. On inspection her perineum is grossly bloody.

OB Triad

Abruptio Placentae

- Late trimester **painful** bleeding
- Normal placental implantation
- Disseminated intravascular coagulopathy (DIC)

In abruptio placentae, a normally implanted placenta (not in the lower uterine segment) separates from the uterine wall before delivery of the fetus. Separation can be partial or complete.

- Most commonly, bleeding is **overt and external**. In this situation blood dissects between placental membranes exiting out the vagina.
- Less commonly, if bleeding remains **concealed or internal**, the retroplacental hematoma remains within the uterus, resulting in an increase in fundal height over time.

Diagnosis is based on the presence of painful late-trimester vaginal bleeding with a normal fundal or lateral uterine wall **placental implantation** not over the lower uterine segment.

Clinical Presentation. Abruptio placentae is the most common cause of late-trimester bleeding (1% of pregnancies at term). It is the most common cause of painful late-trimester bleeding. Classification is made as follows:

- With **mild abruption**, vaginal bleeding is minimal with no fetal monitor abnormality. Localized uterine pain and tenderness is noted, with incomplete relaxation between contractions.
- With **moderate abruption**, symptoms of uterine pain and moderate vaginal bleeding can be gradual or abrupt in onset. From 25–50% of placental surface is separated. Fetal monitoring may show tachycardia, decreased variability, or mild late decelerations.
- With **severe abruption**, symptoms are usually abrupt with a continuous knife-like uterine pain. More than 50% of placental separation occurs. Fetal monitor shows severe late decelerations, bradycardia, or even fetal death. Severe disseminated intravascular coagulation (DIC) may occur.
- Ultrasound visualization of a retroplacental hematoma may be seen.

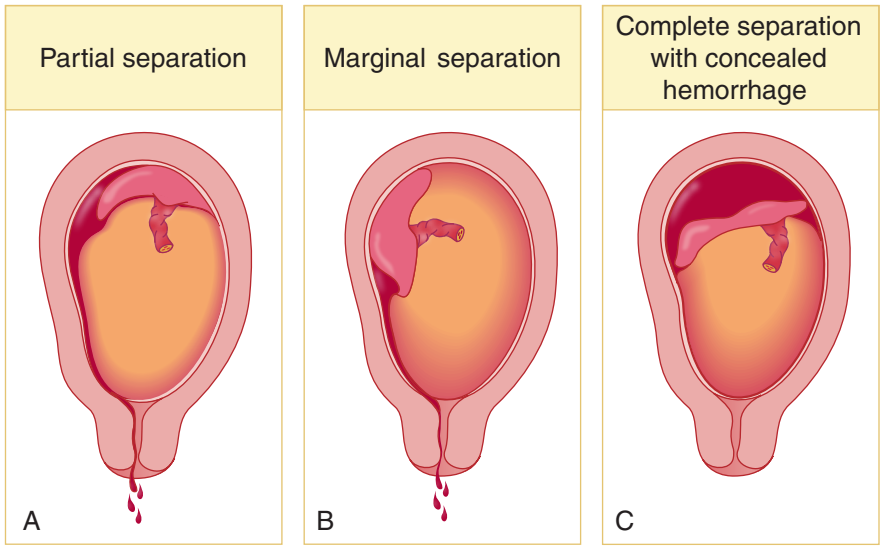

Figure I-6-1. Abruptio Placentae

Abruptio placentae is seen more commonly with **previous abruption**, **hypertension**, and **maternal blunt trauma**. Other risk factors are smoking, maternal cocaine abuse, and premature membrane rupture.

Management is variable:

- **Emergency cesarean delivery** is performed if maternal or fetal jeopardy is present as soon as the mother is stabilized.
- **Vaginal delivery** is performed if bleeding is heavy but controlled or pregnancy is >36 weeks. Perform amniotomy and induce labor. Place external monitors to assess fetal heart rate pattern and contractions. Avoid cesarean delivery if the fetus is dead.
- **Conservative in-hospital observation** is performed if mother and fetus are stable and remote from term, bleeding is minimal or decreasing, and contractions are subsiding. Confirm normal placental implantation with sonogram and replace blood loss with crystalloid and blood products as needed.

Complications include the following:

- Severe abruption can result in hemorrhagic shock with **acute tubular necrosis** from profound hypotension and **DIC** from release of tissue thromboplastin into the general circulation from the disrupted placenta.
- **Couvelaire uterus** refers to blood extravasating between the myometrial fibers, appearing like bruises on the serosal surface.

Placenta previa

> A 34-year-old multigravida at 31 weeks' gestation comes to the birthing unit stating she woke up in the middle of the night in a pool of blood. She denies pain or uterine contractions. Examination of the uterus shows the fetus to be in transverse lie. Fetal heart tones are regular at 145 beats/min. On inspection her perineum is grossly bloody.

OB Triad

Placenta Previa

- Late trimester bleeding
- Lower segment placental implantation
- No pain

Placenta previa occurs when the placenta is implanted in the **lower uterine segment**. This is common early in the pregnancy, but is not typically associated with bleeding.

- Usually the lower implanted placenta atrophies and the upper placenta hypertrophies, resulting in **migration of the placenta**. At term, placenta previa is found in only 0.5% of pregnancies.
- Symptomatic placenta previa occurs when painless vaginal bleeding develops through avulsion of the anchoring villi of an **abnormally implanted** placenta as lower uterine segment stretching occurs in the latter part of pregnancy.

Diagnosis is based on the presence of **painless** late-trimester vaginal bleeding with an obstetric ultrasound showing placental implantation over the **lower uterine segment**. Classification is made as follows:

- **Total, complete, or central previa** is found when the placenta completely covers the internal cervical os. This is the most dangerous location because of its potential for hemorrhage.
- **Partial previa** exists when the placenta partially covers the internal os.
- **Marginal or low-lying previa** exists when the placental edge is near but not over the internal os.

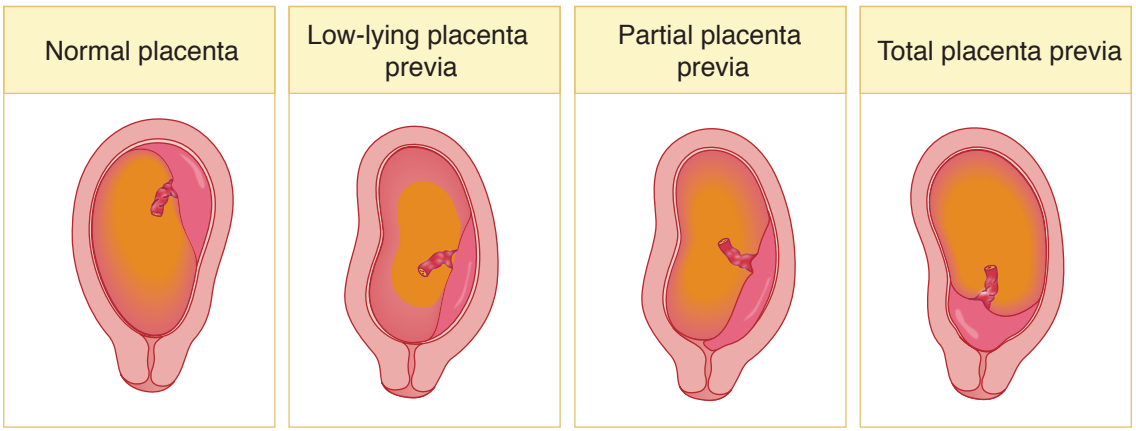

Figure I-6-2. Placenta Previa

Clinical Presentation. The classic picture is **painless** late-pregnancy bleeding, which can occur during rest or activity, suddenly and without warning. It may be preceded by trauma, coitus, or pelvic examination. The uterus is nontender and nonirritable.

Risk Factors. Placenta previa is seen more commonly with **previous placenta previa** and **multiple gestation**. Other risk factors are multiparity and advanced maternal age.

Management is variable:

- **Emergency cesarean delivery** is performed if maternal or fetal jeopardy is present after stabilization of the mother.
- **Conservative in-hospital observation** (bed rest) is performed in preterm gestations if mother and fetus are stable and remote from term. The initial bleed is rarely severe. Confirm abnormal placental implantation with sonogram and replace blood loss with crystalloid and blood products as needed.
- **Scheduled cesarean delivery** is performed if the mother has been stable after fetal lung maturity has been confirmed by amniocentesis, usually at 36 weeks' gestation.

Complications can include:

- If placenta previa occurs over a previous uterine scar, the villi may invade into the deeper layers of the decidua basalis and myometrium, resulting in intractable bleeding requiring **cesarean hysterectomy**.
- Profound hypotension can cause anterior pituitary necrosis (**Sheehan's syndrome**) or **acute tubular necrosis**.

Uncommon Causes

High-Yield

Morbidly adherent placenta

Normally, placental villi invade only the superficial layers of the endometrial decidua basalis. When the villi invade too deeply into the wall of the uterus, the condition is known as placenta accreta, placenta increta, or placenta percreta, depending on the depth of the invasion.

Approximately 1 in 2,500 pregnancies experience placenta accreta, increta, or percreta.

- **Placenta accreta** (**most common**, 80% of cases) occurs when the villi invade the deeper layers of the endometrial decidua basalis but do not penetrate the myometrium.
- **Placenta increta** (15% of cases) occurs when the villi invade the myometrium but do not reach the uterine serosal surface or the bladder.
- **Placenta percreta** (5% of cases) occurs when the villi invade all the way to the uterine serosa or into the bladder.

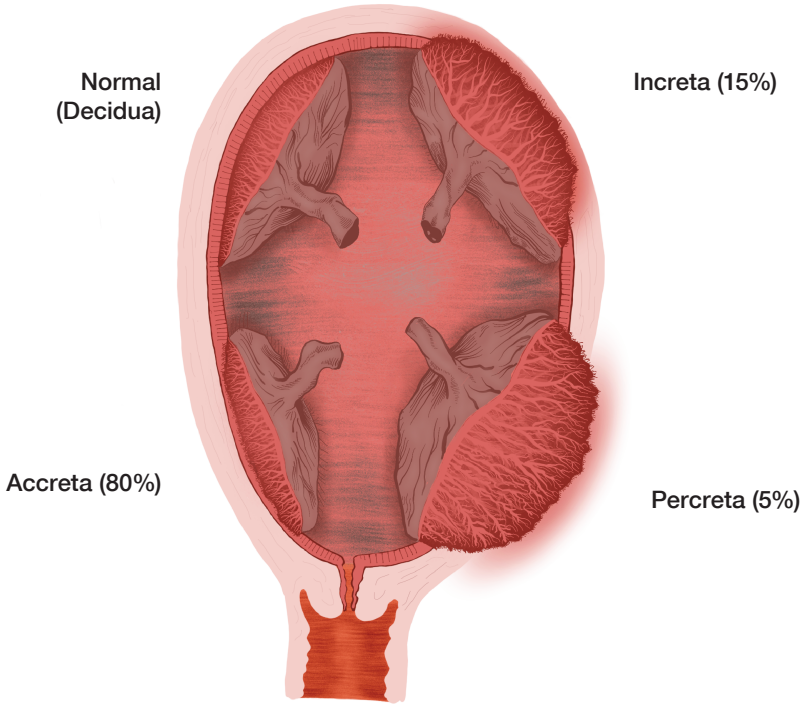

Figure I-6-3. Placenta Accreta

OB Triad

Abnormal Placental Invasion

- **Accreta:** deeper layers decidua basalis
- **Increta:** myometrium not complete
- **Percreta:** uterine serosa or bladder

Vasa previa

A 21-year-old primigravida at 38 weeks' gestation is admitted to the birthing unit at 6-cm dilation with contractions occurring every 3 min. Amniotomy (artificial rupture of membranes) is performed, resulting in sudden onset of bright red vaginal bleeding. The electronic fetal monitor tracing, which had showed a baseline fetal heart rate (FHR) of 135 beats/min with accelerations, now shows a bradycardia at 70 beats/min. The mother's vital signs are stable with normal blood pressure and pulse.

OB Triad

Vasa Previa

- Amniotomy–AROM
- Painless vaginal bleeding
- Fetal bradycardia

Vasa previa is present when fetal vessels traverse the fetal membranes over the internal cervical os. These vessels may be from either a velamentous insertion of the umbilical cord or may be

joining an accessory (succenturiate) placental lobe to the main disk of the placenta. If these fetal vessels rupture the bleeding is from the fetoplacental circulation, and fetal exsanguination will rapidly occur, leading to fetal death.

Diagnosis. This is rarely confirmed before delivery but may be suspected when antenatal sonogram with color-flow Doppler reveals a vessel crossing the membranes over the internal cervical os. The diagnosis is usually confirmed after delivery on examination of the placenta and fetal membranes.

Clinical Presentation. The **classic triad** is rupture of membranes and **painless** vaginal bleeding, followed by fetal bradycardia.

Vasa previa is seen more commonly with **velamentous insertion** of the umbilical cord, **accessory placental lobes**, and multiple gestation.

Management. Immediate cesarean delivery of the fetus is essential or the fetus will die from hypovolemia.

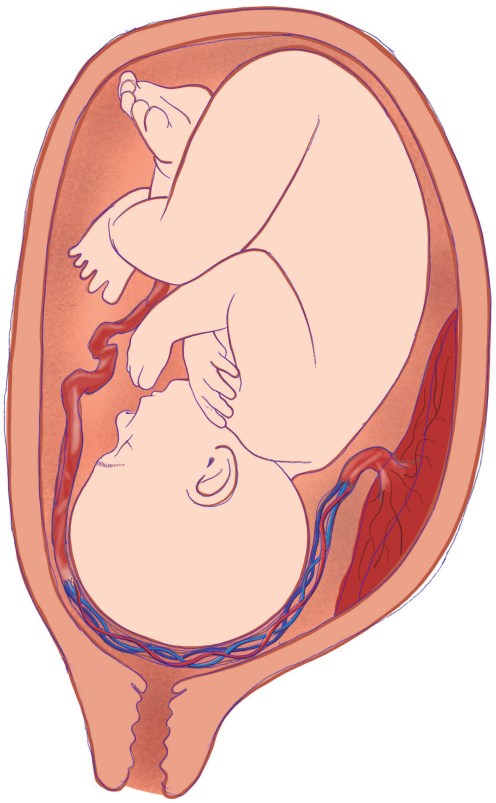

Figure I-6-4. Vasa Previa

Uterine rupture

A 27-year-old G2 P1 woman comes to the maternity unit for evaluation for regular uterine contractions at 34 weeks' gestation. Her previous delivery was an emergency cesarean section at 32 weeks because of hemorrhage from placenta previa. A classical uterine incision was used because of lower uterine segment varicosities. Pelvic exam shows the cervix to be closed and long. As she is being evaluated, she experiences sudden abdominal pain, profuse vaginal bleeding, and fetal bradycardia. Uterine contractions cannot be detected. The fetal head, which was at –1 station, now is floating.

Uterine rupture is **complete separation** of the wall of the pregnant uterus with or without expulsion of the fetus that endangers the life of the mother or the fetus, or both. The rupture may be **incomplete** (not including the peritoneum) or **complete** (including the visceral peritoneum).

Clinical Presentation. The most common findings are vaginal bleeding, loss of electronic fetal heart rate signal, abdominal pain, and loss of station of fetal head. Rupture may occur both before labor as well as during labor.

Diagnosis. Confirmation of the diagnosis is made by **surgical exploration** of the uterus and identifying the tear.

The most common risk factors are previous **classic uterine incision**, **myomectomy**, and excessive oxytocin stimulation. Other risk factors are grand multiparity and marked uterine distention.

A vertical fundal uterine scar is 20 times more likely to rupture than a low segment incision. Maternal and perinatal mortality is also much higher with the vertical incision rupture.

Management. Treatment is surgical. **Immediate delivery** of the fetus is imperative. Uterine repair is indicated in a stable young woman to conserve fertility. Hysterectomy is performed in the unstable patient or one who does not desire further childbearing.

OB Triad

Uterine Rupture

- Late trimester painful bleeding
- Previous uterine incision
- High perinatal mortality

Perinatal Infections 7

Learning Objective

- ❑ Describe the route of transmission and common complications of perinatal infections including group B beta-hemolytic streptococci, toxoplasmosis, varicella zoster, rubella, cytomegalovirus, HSV, HIV, syphilis, and hepatitis B

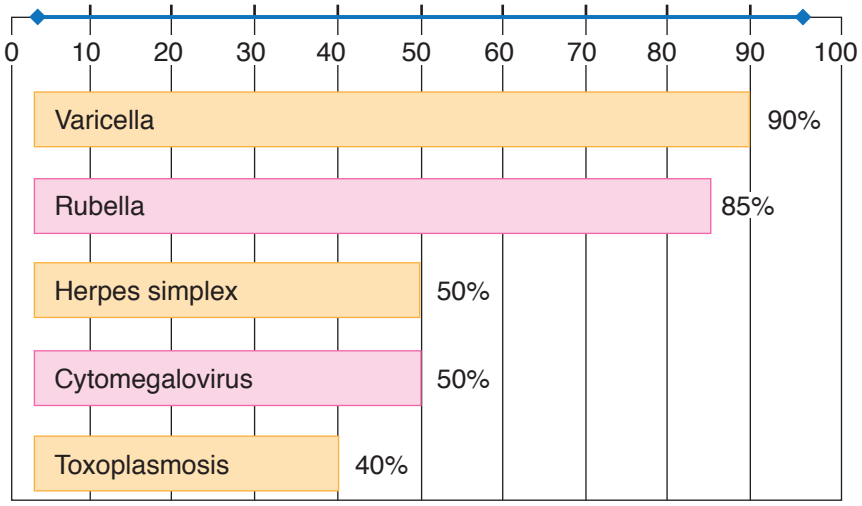

Figure I-7-1. Prevalence of IgG Seropositivity in Pregnant Women

NONSEXUALLY TRANSMITTED

Group B β-Hemolytic Streptococci

High-Yield

A 20-year-old woman G2 P1 is admitted to the birthing unit at 35 weeks' gestation in active labor at 6 cm dilation. Her prenatal course was unremarkable, with the exception of a positive first-trimester urine culture for GBS. Her first baby was hospitalized for 10 days after delivery for GBS pneumonia.

OB Triad

GBS Neonatal Sepsis

- Newborn sepsis
- Within hours of birth
- Bilateral diffuse pneumonia

Group B β-hemolytic streptococci (GBS) is a bacterium commonly found in normal GI tract flora (30% of women have asymptomatic **vaginal colonization** with GBS, with the majority having intermittent or transient carrier status). Most neonates delivered to colonized mothers will be culture positive. The significance of this is that **1 in 500 neonates** will develop serious clinical infections or sepsis.

- **Early onset** infection is the most common finding, occurring within a few hours to days of birth, and is characterized by fulminant **pneumonia and sepsis**. This is usually vertical transmission from mother to neonate, with a 30% mortality rate at or before 33 weeks but <5% at term.
- **Late-onset** infection is less common, occurring after the first week of life, and is characterized by meningitis. This is usually hospital acquired, with a 5% mortality rate.

Prevention is to decrease early-onset infection only. Intrapartum antibiotic prophylaxis of neonatal GBS sepsis is given with IV penicillin G. If the patient is penicillin-allergic, use clindamycin or vancomycin.

Candidates for antibiotic prophylaxis are selected as follows:

- **No screening:** All women with a positive GBS urine culture or a previous baby with GBS sepsis will receive intrapartum prophylaxis. Prophylaxis of other women is based on either of the following two protocols, each of which will prevent 70% of neonatal sepsis.
- **Screening by vaginal culture:** Third-trimester vaginal and rectal cultures are obtained at 36 0/7 to 37 6/7 weeks gestational age, and intrapartum prophylaxis is administered only to those with positive GBS cultures. Antepartum treatment is not given.
- **Screening by intrapartum risk factors:** No vaginal cultures are obtained. Intrapartum prophylaxis is given on the basis of risk factors being present: preterm gestation (<37 weeks), membranes ruptured >18 h, or maternal fever (≥100.4°F) (38°C).

Toxoplasmosis

High-Yield

A 26-year-old primigravida was admitted to the birthing unit at 39 weeks' gestation in active labor at 6 cm dilation. During her second trimester she experienced a mononucleosis-like syndrome. Uterine fundal growth lagged behind that expected on the basis of a first-trimester sonogram. Serial sonograms showed symmetrical intrauterine growth retardation (IUGR). She delivered a 2,250 g male neonate who was diagnosed with microcephaly, intracranial calcifications, and chorioretinitis.

OB Triad

Congenital *Toxoplasmosis*

- Chorioretinitis
- Intracranial calcifications
- Symmetrical IUGR

Note

Remember to distinguish between *intracranial* calcifications with *Toxoplasma* and *periventricular* calcifications with CMV.

Toxoplasmosis is caused by a **parasite** (*Toxoplasma gondii*) transmitted most commonly in the United States from exposure to infected **cat feces**. Infections can also occur from drinking raw goat milk or eating raw or undercooked infected meat.

- **Vertical transmission** from mother to fetus or neonate can only occur during the parasitemia of a primary infection because the result is residual lifelong immunity.
- Up to 40% of pregnant women are toxoplasmosis IgG seropositive.
- First-trimester infection risk is **low** (15%), but infections are **most serious**, even lethal.
- Third-trimester infection risk is **high** (50%), but infections are **mostly asymptomatic**.

Significance.

- **Fetal infection:** Manifestations may include symmetric IUGR, nonimmune fetal hydrops, microcephaly, and **intracranial calcifications**.
- **Neonatal presentation:** Manifestations may include **chorioretinitis**, seizures, hepatosplenomegaly, and thrombocytopenia.

Prevention includes avoidance of infected cat feces, raw goat milk, and undercooked meat.

Treatment. Pyrimethamine and sulfadiazine for known infections; spiramycin to prevent vertical transmission from the mother to the fetus.

Varicella

High-Yield

A 29-year-old woman (G2 P1) is at 34 weeks' gestation. She complains of uterine contractions every 5 min. During the last few days she has developed diffuse pruritic vesicles on her neck that appear to be also developing on her chest and breasts. She has a fever and complains of malaise.

Varicella zoster (VZV) is a DNA virus that is the causative agent of chicken pox and herpes zoster. It is spread by **respiratory droplets**, but is less contagious than rubeola or rubella. By adulthood, >90% of women are immune.

Significance.

- **Fetal infection:** Transplacental infection rate is as low as 2%, with 25% mortality.
- **Neonatal presentation:** Congenital varicella syndrome is characterized by "zigzag" skin lesions, mulberry skin spots, optic atrophy, cataracts, chorioretinitis, extremity hypoplasia, and motor and sensory defects. The greatest neonatal risk is if maternal rash appears between 5 days antepartum and 2 days postpartum. No passive IgG antibodies are present.
- **Maternal infection:** 10% of patients with varicella will develop **varicella pneumonia**, which has a high maternal morbidity and mortality. Communicability begins 1–2 days before vesicles appear and lasts until all vesicles are crusted over. Pruritic vesicles begin on the head and neck, progressing to the trunk. The infection can trigger labor.

Prevention includes administration of VZIG (varicella zoster immune globulin) to a susceptible gravida within 96 h of exposure. Live-attenuated varicella virus (Varivax III) can be administered to nonpregnant or postpartum to varicella IgG-antibody-negative women.

Treatment. IV antiviral treatment with **acyclovir** for varicella pneumonia, encephalitis, or the immunocompromised.

OB Triad

Congenital Varicella

- "Zig-zag" skin lesions
- Microphthalmia
- Extremity hypoplasia

Rubella

High-Yield

An 18-year-old primigravida is at 30 weeks' gestation and is employed in a childcare center. One of the children had a rash that was diagnosed as rubella. The patient's rubella IgG titer is negative. She is concerned about the possibility of her fetus getting infected with rubella.

OB Triad

Congenital Rubella

- Congenital deafness
- Congenital cataracts
- Congenital heart disease

Rubella is a highly contagious RNA virus that is spread by **respiratory droplets**. Up to 85% of pregnant women are rubella IgG seropositive. **Vertical transmission** from mother to fetus or neonate can only occur during the viremia of a primary infection because the result is residual lifelong immunity.

- **Fetal infection:** Transplacental infection rate is >90% in first 10 weeks of pregnancy, but 5% in third trimester. Manifestations may include symmetric IUGR, microcephaly, or ventriculoseptal defect (VSD).
- **Neonatal infection:** Congenital rubella syndrome is characterized by **congenital deafness** (**most common** sequelae), **congenital heart disease**, **cataracts**, intellectual disability, hepatosplenomegaly, thrombocytopenia, and "blueberry muffin" rash.
- **Maternal infection:** Rubella infection during pregnancy is generally a mild, low-morbidity condition.

Note

Rubella has been eradicated from the United States; since 2004, no cases have been reported.

Prevention includes rubella IgG antibody screening for all pregnant women. Rubella-susceptible women should avoid known rubella cases, then receive active immunization after delivery. Because rubella vaccine is made using a live attenuated virus, pregnancy should be avoided for one month after immunization.

Treatment. No specific treatment is available.

Coxsackie Virus

Coxsackie is an enterovirus commonly known as hand, foot and mouth disease (HFMD). It is common, and pregnant women are frequently exposed to it, especially in summer and fall months. Infections are spread by fecal-oral and respiratory routes, with the majority of infections mild or asymptomatic mostly affecting children.

- **Fetal infection:** Enteroviruses rarely cross the placenta and cause disease in the fetus. There is no evidence of infection causing increased miscarriages, stillbirths, or malformations. Vertical transmission may occur at birth with exposure of the fetus to virus-containing maternal secretions.
- **Neonatal presentation:** Newborns who acquire infection from mothers at delivery are at risk of severe disease including sepsis, encephalitis, myocarditis, and pneumonia.
- **Maternal infection:** Most enterovirus infections during pregnancy cause mild or no illness in the mother. Clinical findings, when they occur, can include fever, oral vesicles of the mouth and tongue, as well as lesions on the hands and feet. Infection in the third trimester can trigger labor.

Prevention includes avoiding individuals with possible disease. Maintain good handwashing practices and wear a mask if contact with an infected person is unavoidable.

Treatment. No specific therapy is available.

Parvovirus B19

High-Yield

Parvovirus B-19 is a DNA virus also known as fifth disease. It is a common childhood illness characterized by a "slapped cheek" appearance on the face. When infection occurs in adults it is most often asymptomatic or mild. It preferentially infects rapidly dividing cells such as RBC precursors and stimulates apoptosis or cell death. About 50% pregnant woman have protective IgG antibodies. Vertical transmission is transplacental at the time of primary viremia.

- **Fetal infection:** Almost all fetal losses are linked to infections occurring prior to 20 weeks. Parvovirus B-19 is cytotoxic to fetal RBC precursors and may cause fetal anemia and hydrops fetalis. This nonimmune hydrops is seen more commonly with infections prior to 32 weeks. Transient isolated fetal pleural or pericardial effusions may be seen that resolve spontaneously prior to delivery. The effusions are thought to be due to direct cardiac/pleural inflammation.
- **Neonatal presentation:** While fetal hydrops can occur, most intrauterine parvovirus infections do not have an adverse outcome. There is no evidence of teratogenicity.
- **Maternal infection:** Maternal parvovirus B-19 infections are mild and generally do not include the rash seen in children. Joint pains and fever may occur but the clinical course is usually self-limited.

Prevention. Pregnant women exposed to or with symptoms of parvovirus infection should have serologic testing for IgG and IgM antibodies.

- A positive IgG and negative IgM is consistent with maternal immunity so the fetus is protected.
- A positive IgM antibody is consistent with acute infection and should initiate obstetric ultrasound assessment starting at 22 weeks, looking for evidence of fetal hydrops as well as fetal Doppler screening for anemia.

Treatment. Intrauterine transfusion for severe fetal anemia (only intervention available).

Zika Virus

High-Yield

Zika virus is a mosquito-borne RNA flavivrus. Vertical transmission is transplacental; however, because the virus can persist longer in the serum of a pregnant woman as compared to that of one who is not, the fetus is at risk for infection and major CNS anomalies even if the mother is asymptomatic.

- **Fetal infection:** The greatest risk of serious perinatal sequelae appears to be with 1st and 2nd trimester infections. Ultrasound abnormalities seen with congenital infections include fetal growth restriction, ventriculomegaly, microcephaly, and intracranial calcifications.
- **Neonatal presentation:** Newborn findings other than listed above include ocular abnormalities (e.g. retinal atrophy, microphthalmia), hearing loss, and neurologic abnormalities (e.g. hypertonia, hypotonia, seizures).
- **Maternal infection:** Clinical signs consistent with Zika infection are maculopapular rash, arthralgias, conjunctivitis and fever. Only 20% of infected women will have these findings which are often mild. Zika can also be transmitted though sex without a condom with an infected person even if there are no symptoms.

Prevention. Pregnant women in endemic areas should follow steps to prevent mosquito bites. Avoid unprotected sex with an infected partner. Symptomatic or Zika-exposed women should undergo serum and urine nucleic acid test and IgM serology as soon as possible through 12 weeks after. Positive blood tests should be followed up by prenatal ultrasound and repeated monthly looking for findings listed above.

Treatment. No specific maternal treatment.

SEXUALLY TRANSMITTED

OB Triad

Cytomegalovirus

- Most common congenital viral syndrome
- Most common cause of deafness in children
- Neonatal thrombocytopenia and petechiae

Cytomegalovirus

High-Yield

A 31-year-old neonatal intensive care unit nurse has just undergone an uncomplicated term spontaneous vaginal delivery of a 2,300 g female neonate with a diffuse petechial rash. At 12 weeks' gestation she experienced a flulike syndrome with right upper quadrant pain. Obstetric sonograms showed fetal growth was only at the fifth percentile.

Cytomegalovirus (CMV) is a DNA herpes virus that is spread by infected body secretions. Up to 50% of pregnant women are CMV IgG seropositive. Vertical transmission from mother to fetus or neonate occurs mainly during the viremia of a primary infection. However, because the result of primary infection is predisposition to a residual lifelong latency, fetal infection can occur with reactivation.

Significance.

- **Fetal infection:** Transplacental infection rate is 50% with maternal primary infections regardless of the pregnancy trimester, but <1% with recurrent infections. Manifestations may include nonimmune hydrops, symmetric IUGR, microcephaly, and cerebral calcifications in a periventricular distribution.
- **Neonatal infection:** From 1–2% of newborns have evidence of in utero exposure to CMV. Congenital CMV syndrome is the **most common** congenital viral syndrome in the United States. CMV is the **most common** cause of sensorineural deafness in children. Only 10% of infected infants have clinical disease, which includes **petechiae**, mulberry skin spots, meningoencephalitis, periventricular calcifications, hepatosplenomegaly, thrombocytopenia, and jaundice.
- **Maternal infection:** CMV infection during pregnancy is generally a mild, low-morbidity condition appearing as a mononucleosis-like syndrome with hepatitis.

Prevention includes following universal precautions with all body fluids. Avoid transfusion with CMV-positive blood.

Treatment. Antiviral therapy with ganciclovir

Herpes Simplex Virus

High-Yield

A 21-year-old multipara was admitted to the birthing unit at 39 weeks' gestation in active labor at 6 cm dilation. The bag of water is intact. She had a history of genital herpes preceding the pregnancy. Her last outbreak was 8 weeks ago. She now complains of pain and pruritis. On examination she had localized, painful, ulcerative lesions on her right vaginal wall.

Herpes simplex virus (HSV) is a DNA herpes virus that is spread by intimate **mucocutaneous contact**. Up to 50% of pregnant women are HSV IgG seropositive.

- Most genital herpes results from HSV II, but can also occur with HSV I.
- Transplacental transmission from mother to fetus can occur with viremia during the primary infection but is rare. HSV infection predisposes to a residual lifelong latency with periodic recurrent attacks. The most common route of fetal infection is contact with **maternal genital lesions** during a recurrent HSV episode.

Diagnosis. The definitive diagnosis is a positive HSV culture from fluid obtained from a ruptured vesicle or debrided ulcer, but there is a 20% false-negative rate. PCR is 2–4x more sensitive and is best to detect viral shedding.

Significance.

- **Fetal infection:** The transplacental infection rate is 50% with maternal primary infections. Manifestations may include spontaneous abortions, symmetric IUGR, microcephaly, and cerebral calcifications.
- **Neonatal infection:** With passage through an HSV-infected birth canal, the neonatal attack rate is 50% with a primary infection, but <5% with a recurrent infection. Neonatal mortality rate is 50%. Those who survive have severe sequelae: meningoencephalitis, intellectual disability, pneumonia, hepatosplenomegaly, jaundice, and petechiae.
- **Maternal infection** (two types):
  - **Primary herpes** results from a viremia and has systemic manifestations: fever, malaise, adenopathy, and diffuse genital lesions (vagina, cervix, vulva, and urethra). Transplacental fetal infection is possible; however, in 2/3 of cases the infection is mild or subclinical.
  - **Recurrent herpes** results from migration of the virus from the dorsal root ganglion but is localized and less severe, with no systemic manifestations. Fetal infection results only from passing through a birth canal with lesions present.

Prevention includes performing a cesarean section in the presence of genital HSV lesions at the time of labor. (If membranes have been ruptured >8–12 h, the virus may already have infected the fetus and cesarean delivery would be of no value.)

Treatment. Acyclovir.

Human Immunodeficiency Virus

High-Yield

A 22-year-old multigravida is a former IV drug user. She was diagnosed as HIV positive 12 months ago during her previous pregnancy. She underwent vaginal delivery of an infant who is also HIV positive. She is now pregnant again at 15 weeks' gestation.

Human immunodeficiency virus (HIV) is an RNA retrovirus spread by infected body secretions. Sharing contaminated needles, having sexual intercourse with an infected partner, and perinatal transmission are the most common modes of transmission.

The infected patient develops acquired immunodeficiency syndrome **(AIDS)**. The clinical course from HIV to AIDS is a gradual but relentless immunosuppression during a period of years, resulting in death caused by overwhelming infection from opportunistic diseases.

Significance.

- **Fetal infection:** Transplacental infection occurs, but the major route of vertical transmission is contact with infected genital secretions at the time of vaginal delivery. Without maternal azidothymidine (AZT) prophylaxis, the vertical transmission rate is 30%, but with AZT the infection rate drops to 10% with vaginal delivery. With elective cesarean section without labor and before membrane rupture, the perinatal infection rate may be <5%. The greatest benefit to the fetus of cesarean delivery is probably in women with low CD4 counts and high RNA viral loads, making infection through a vaginal delivery much more likely.
- **Neonatal infection:** At birth neonates of HIV-positive women will have positive HIV tests from transplacental passive IgG passage. HIV-infected breast milk can potentially transmit the disease to the newborn. Progression from HIV to AIDS in infants is more rapid than in adults.
- **Maternal infection:** Pregnancy in an HIV-positive woman does not enhance progression to AIDS.

Prevention includes the following:

- **Antiviral prophylaxis:** The U.S. Public Health Service recommends that HIV-infected pregnant women be offered combination treatment with HIV-fighting drugs to help protect their health and prevent passing the infection on to their babies. Infected pregnant women should take triple-drug therapy including the drug zidovudine (ZDV) as part of their drug regimen, starting at 14 weeks and continuing throughout pregnancy, intrapartum, and after delivery.
- **Mode of delivery:** Vaginal delivery should be planned at 39 weeks, with the following guidelines:
  - Avoid amniotomy as long as possible.
  - Do not use scalp electrodes in labor.
  - Avoid forceps or vacuum extractor operative delivery.
  - Use gentle neonatal resuscitation.
  - If viral load ≥1,000 copies/mL, offer cesarean section at 38 weeks without amniocentesis.
- **Breast feeding** should probably be avoided in HIV-positive women.
- **Universal precautions:** Pay careful attention to handling of all body fluids.

Treatment. Combination triple anti-viral HAART therapy for all HIV-positive pregnant women; this includes 2 nucleotide reverse transcriptase inhibitors (NRTIs) with an NNRTI or a protease inhibitor (e.g., zidovudine, lamivudine, or ritonavir).

Syphilis

High-Yield

A 34-year-old multigravida presents for prenatal care in the second trimester. She admits to a past history of substance abuse but states she has been clean for 6 months. With her second pregnancy, she experienced a preterm delivery at 34 weeks' gestation of a male neonate who died within the first day of life. She states that at delivery the baby was swollen with skin lesions and that the placenta was very large. She was treated with antibiotics but she does not remember the name or other details. On a routine prenatal panel with this current pregnancy she is found to have a positive VDRL (Venereal Disease Research Laboratory) test.

Syphilis is caused by *Treponema pallidum*, a motile anaerobic spirochete that cannot be cultured. Syphilis does *not* result in a state of immunity or latency; the infection can be eradicated by appropriate treatment but reinfection can occur over and over again. It is spread as a sexually transmitted disease by intimate contact between moist mucous membranes or congenitally through the placentae to a fetus from an infected mother.

Significance.

- **Fetal infection:** Transplacental infection is common with vertical transmission rates of 60% in primary and secondary syphilis. The rate of fetal infection with latent or tertiary syphilis is lower. Without treatment, manifestations of early congenital syphilis include nonimmune hydrops, macerated skin, anemia, thrombocytopenia, and hepatosplenomegaly. Fetal death rates are high, with perinatal mortality rates approaching 50%. The placenta is typically large and edematous.
- **Neonatal infection:** Late congenital syphilis is diagnosed after age 2 years and includes "Hutchinson" teeth, "mulberry" molars, "saber" shins, "saddle" nose, and 8th nerve deafness.
- **Maternal infection** (four types):
  - **Primary syphilis** is the first stage after infection. Papules become painless ulcers with rolled edges (chancres) which appear 2–3 weeks after contact at the site of infection, most commonly the vulva, vagina, or cervix. Darkfield microscopy of lesion exudate is positive for the spirochete, but the nonspecific serologic tests VDRL or rapid plasma reagin [**RPR**] test) are not yet positive. Without treatment the chancre spontaneously disappears.
  - **Secondary syphilis** is characterized by systemic spirochetemia. Around 2–3 months after contact, fever, malaise, general adenopathy, and a maculopapular skin rash ("money spots") are seen. Broad exophytic excrescences (**condyloma lata**) appear on the vulva. These physical findings also spontaneously disappear without treatment. Darkfield microscopy of condyloma exudate is positive for treponema. The VDRL or RPR test will be positive, but a diagnosis of syphilis must be confirmed with a treponema-specific test, such as the fluorescent titer antibody absorption (FTA-ABS) or microhemagglutination assay for antibodies to *T. pallidum* (MHA-TP). The treponema-specific tests do not correlate with disease activity and remain positive in spite of treatment.
  - **Latent syphilis** is characterized by absence of symptoms or physical findings. The nonspecific and treponema-specific tests remain positive. Around 35% of cases proceed to tertiary disease.
  - **Tertiary syphilis** is a symptomatic stage with symptoms dependent on which organ system is affected by the classic necrotic, ulcerative nodules (**gummas**). Lesion location may include the cardiovascular system (aortitis, saccular aneurysms), CNS (meningitis, tabes dorsalis, dementia, ataxia), or bone (osteitis). Not only are the blood tests positive, but also the cerebrospinal fluid will be positive with CNS involvement.

Table I-7-1. Syphilis in Pregnancy

Characteristic	Primary	Secondary
Classic lesion	Chancre	Condyloma lata ("money spots")
Extent of disease	Localized	Systemic
Lab tests (VDRL, Darkfield, FTA-ABS)	VDRL (–) Darkfield (+) FTA-ABS (+)	VDRL (+) Darkfield (+) FTA-ABS (+)
Fetal infection rate	60%	60%
Treatment of choice	Penicillin	Penicillin

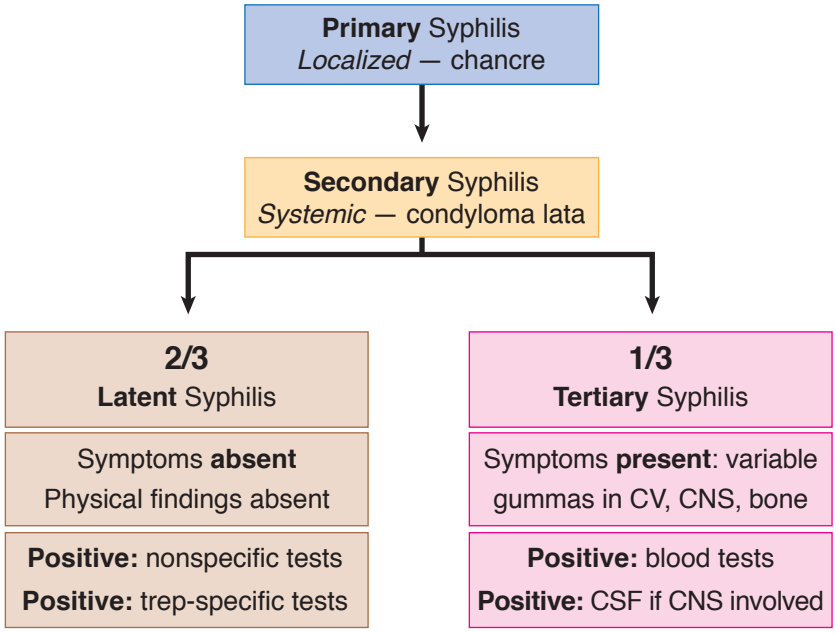

Figure I-7-2. Maternal Syphilis

Prevention includes the following:

- Vaginal delivery is appropriate with cesarean section only for obstetric indications.
- Follow the principles of avoiding multiple sexual partners, and promote use of barrier contraceptives.

Management. Benzathine penicillin 2.4 million units IM × 1 in pregnancy to ensure adequate antibiotic levels in the fetus (other antibiotics do not cross the placentae well). Even if the gravida is penicillin-allergic, still give a full penicillin dose using an oral desensitization regimen under controlled conditions.

Follow serology titers at 1, 3, 6, 12, and 24 months. Decrease titers fourfold by 6 months; they should be negative in 12–24 months.

The **Jarisch-Herxheimer reaction** is associated with treatment and occurs in 50% of pregnant women. It starts in 1–2 hours, peaks in 8 hours, and resolves in 24–48 hours. It is associated with acute fever, headache, myalgias, hypotension, and uterine contractions. Management is supportive care.

Hepatitis B

High-Yield

> A 29-year-old multigravida was found on routine prenatal laboratory testing to be positive for hepatitis B surface antigen. She is an intensive care unit nurse. She received 2 units of packed red blood cells two years ago after experiencing postpartum hemorrhage with her last pregnancy.

Hepatitis B (HBV) is a DNA virus that is spread by infected body secretions. Sharing contaminated needles, having sexual intercourse with an infected partner, and perinatal transmission are the most common ways of transmission. Vertical transmission accounts for 40% of all chronic HBV infections. Most HBV infections are asymptomatic.

Significance.

- **Fetal infection:** Transplacental infection is rare, occurring mostly in the third trimester. The main route of fetal or neonatal infection arises from exposure to or ingestion of infected genital secretions at the time of vaginal delivery. There is no perinatal transmission risk if the mother is positive for HBV surface antibodies but negative for HBV surface antigen.
- **Neonatal infection:** Neonatal HBV develops in only 10% of mothers positive for HBsAg but in 80% of those positive for both HBsAg and HBeAg. Of those neonates who get infected, 80% will develop chronic hepatitis, compared with only 10% of infected adults.
- **Maternal infection** (3 types):
  - **Asymptomatic HBV:** The majority of all infected patients fall into this category with no impact on maternal health. Hepatitis B surface antigen (HBsAg) is the screening test used for identifying existing infection and is obtained on all pregnant women. A positive HBsAg test is followed up with a complete hepatitis panel and liver enzymes assessing for active or chronic hepatitis.
  - **Acute hepatitis:** Acute and chronic HBV infections can result in right upper quadrant pain and lethargy varying according to the severity of the infection. Laboratory studies show elevated bilirubin and high liver enzymes. The majority of patients with acute hepatitis will recover normal liver function.
  - **Chronic hepatitis:** Cirrhosis and hepatocellular carcinoma are the most serious consequences of chronic hepatitis.

Prevention includes:

- Vaginal delivery is indicated with cesarean section only for obstetric indications.
- Avoid scalp electrodes in labor as well as scalp needles in the nursery. Neonates of HBsAg-positive mothers should receive passive immunization with hepatitis B immunoglobulin (HBIg) and active immunization with hepatitis B vaccine. Breast feeding is acceptable after the neonate has received the active immunization and HBIG.
- HBsAg-negative mothers at high risk for hepatitis B should receive HBIg passive immunization. Active immunization is safe in pregnancy because the agent is a killed virus.

Management. No specific therapy for acute hepatitis; interferon or lamivudine for chronic HBV.

Table I-7-2. Perinatal Infections

	Lifelong	Treatment	Delivery
Group β beta streptococcus	Colonization	Penicillin G	Vaginal
Toxoplasmosis	Immunity	Pyrimethamine sulfadiazine	Vaginal
Rubella	Immunity	None	Vaginal
Cytomegalovirus	Latency	Ganciclovir	Vaginal
Varicella/HSV	Latency	Acyclovir	Cesarean section if active HSV
HIV	Latency	Triple Rx antivirals	Cesarean section if high viral load

Table I-7-3. Key Phrases in Perinatal Infections

	Findings	Findings
Toxoplasmosis*+	Intracranial calcifications	Chorioretinitis
Varicella+	Zig zag lesions	Small eyes
Rubella*+	Deafness	Congenital heart disease
Cytomegalovirus*+	Petechiae	Enlarged liver, spleen
Syphilis+	Hydrops	Macerated skin
HSV, HIV, HBV$^{\Delta}$	None	

*Associated with IUGR
+Transplacental vertical transmission
$^{\Delta}$Vaginal delivery vertical transmission

Obstetric Complications 8

Learning Objectives

- ❏ Describe the management of cervical insufficiency and multiple gestation
- ❏ Answer questions about alloimmunization
- ❏ List the management steps for preterm labor, premature rupture of membranes, and post-term pregnancy

CERVICAL INSUFFICIENCY

A 32-year-old primigravida at 18 weeks' gestation comes to the maternity unit complaining of pelvic pressure and increasing vaginal mucus discharge. She denies any uterine contractions. On pelvic examination the fetal membranes are seen bulging into the vagina, and no cervix can be palpated. Fetal feet can be felt through the membranes. Two years ago she underwent a cervical conization for cervical intraepithelial neoplasia.

Cervical insufficiency (or cervical incompetency) has been used to describe the inability of the uterine cervix to retain a pregnancy to viability in the absence of contractions or labor.

- In the past, a diagnosis was made on the basis of a history of painless cervical dilation after the first trimester with expulsion of a previable living fetus.
- Recent studies using U/S to examine cervical length suggest that cervical function is not an all-or-none phenomenon, but may be a continuous variable with a range of degrees of competency that may be expressed differently in subsequent pregnancies.

Causes of cervical insufficiency include trauma from rapid forceful cervical dilation associated with second trimester abortion procedures, cervical laceration from rapid delivery, injury from deep cervical conization, and congenital weakness from diethylstilbestrol (DES) exposure.

Diagnosis. Studies show the benefit of elective cervical cerclage with a history of ≥1 unexplained second-trimester pregnancy losses. However, the benefit of cervical cerclage placement is unclear in the following situations: sonographic findings of a short cervix or funneling, history of cervical surgery, DES exposure. Serial transvaginal ultrasound evaluations of the cervix after 16–20 weeks may be helpful.

OB Triad

Cervical Insufficiency

- Pregnant 18–22 weeks
- Painless cervical dilation
- Delivery of previable fetus

Management. With sonographic demonstration for fetal normality, elective cerclage placement at 13–14 weeks' gestation. With sonographic evidence of cervical insufficiency after ruling out labor and chorioamnionitis, possible emergency or urgent cerclage.

- Consider cerclage if cervical length <25 mm by vaginal sonography prior to 24 weeks and prior preterm birth at <34 weeks gestation.
- **McDonald cerclage** places a removable suture in the cervix. The benefit is that vaginal delivery can be allowed to take place, avoiding a cesarean.
- **Shirodkar cerclage** utilizes a submucosal placement of the suture that is buried beneath the mucosa and left in place. Cesarean delivery is performed at term.
- Cerclage removal should take place at 36–37 weeks, after fetal lung maturity has taken place but before the usual onset of spontaneous labor that could result in avulsion of the suture.

OB Triad

Di–Di–Di or Mono–Di–Di Twins

- Twin pregnancy
- Gender same or unknown
- Two placentas seen

Mono–Mono–Di Twins

- Twin pregnancy
- Gender always same
- *One* placenta but *two* sacs

Mono–Mono–Mono Twins

- Twin pregnancy
- Gender always same
- *One* placenta and *one* sac

MULTIPLE GESTATION

A 21-year-old primigravida at 15 weeks' gestation is seen for a routine prenatal visit. At her last visit four weeks ago, her uterus was appropriate for size and dates. Today, her uterine fundus is palpable at the umbilicus.

Multiple gestation is a pregnancy in which more than one fetus is present. The fetuses may arise from one or more zygotes and are usually separate, but may rarely be conjoined.

Risk Factors.

- **Dizygotic twins** are most common. **Identifiable risk factors** include race, geography, family history, or ovulation induction. Risk of twinning is up to 10% with clomiphene citrate and up to 30% with human menopausal gonadotropin.
- **Monozygotic twins** have **no identifiable risk factors.**

Diagnosis. Obstetric sonogram demonstration of more than one intrauterine fetus.

Complications for all twin pregnancies include nutritional anemias (iron and folate), preeclampsia, preterm labor (50%), malpresentation (50%), cesarean delivery (50%), and postpartum hemorrhage.

Table I-8-1. Complications of Twin Pregnancies

ANTEpartum	Anemia ↑ 3x (iron & folate)
	Preeclampsia ↑ 3x
	Gestational diabetes ↑ 2x
	Thromboembolism ↑ 4x
INTRApartum	Preterm labor (50%)
	Malpresentation (50%)
	Cesarean delivery (50%)
POSTpartum	Hemorrhage ↑ 5x

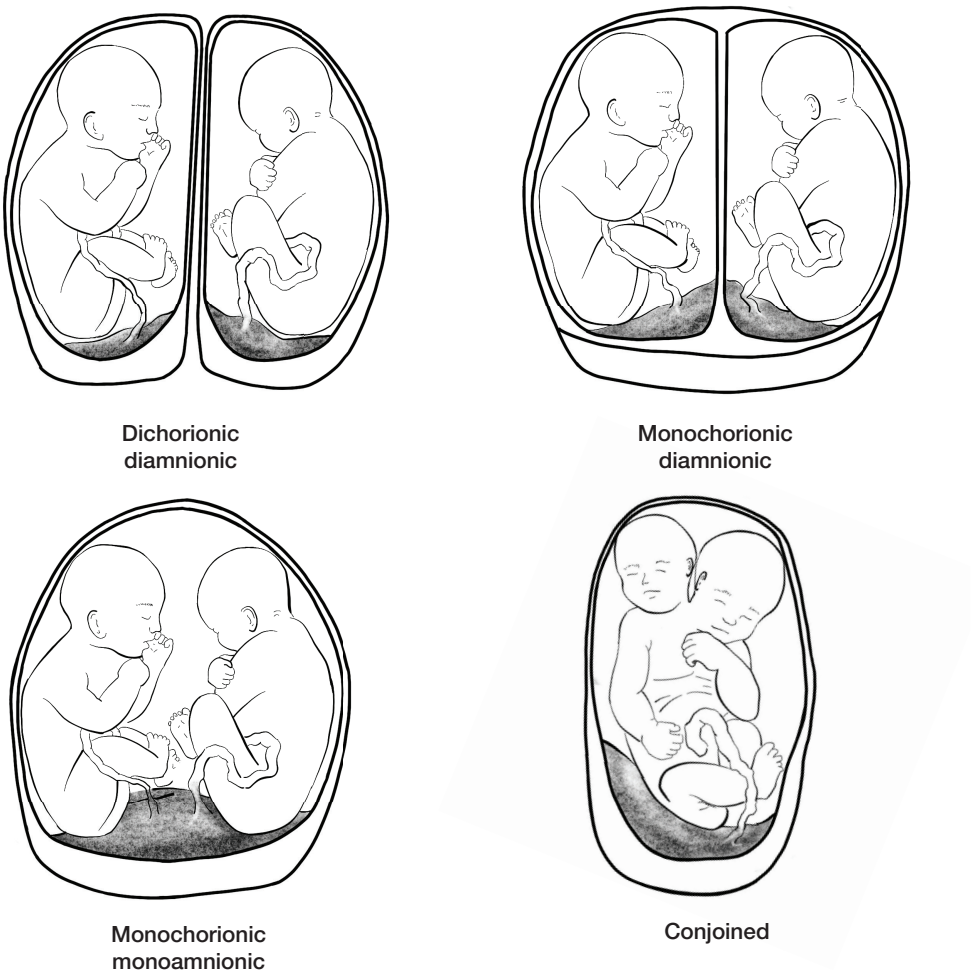

Figure I-8-1. Multiple Gestation

Dizygotic twins arise from multiple ovulation with two zygotes. They are always dichorionic, diamnionic.

Monozygotic twins arise from one zygote. Chorionicity and amnionicity vary according to the duration of time from fertilization to cleavage.

- **Up to 72 hours** (separation up to the morula stage), the twins are **dichorionic, diamnionic.** There are two placentas and two sacs. This is the **lowest** risk of all monozygotic twins.
- **Between 4–8 days** (separation at the blastocyst stage), the twins are **monochorionic, diamnionic**. There is one placenta and two sacs. A specific additional complication is **twin–twin transfusion**, which develops in 15% of mono-di twins. The twins share a single placenta but do so unequally. The donor twin gets less blood supply, resulting in growth restriction, **oligohydramnios**, and anemia. However, neonatal outcome is usually better. The **recipient twin** gets more blood supply, resulting in excessive growth, **polyhydramnios**, and polycythemia. Intrauterine fetal surgery is indicated to laser the vascular connections on the placental surface between the two fetuses. Neonatal course is often complicated.

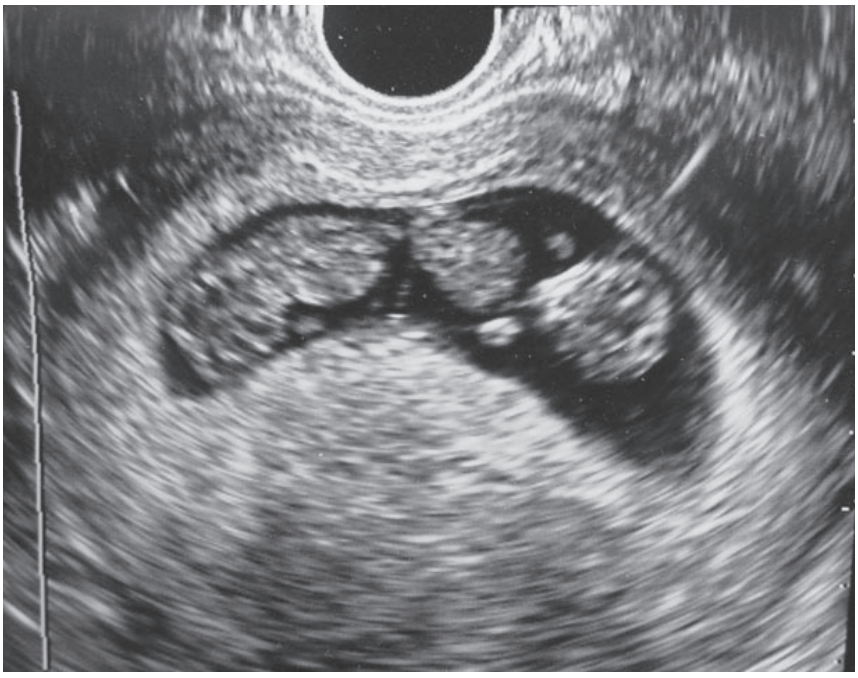

Figure I-8-2. Monochorionic, Diamniotic Twin Gestation

- **Between 9–12 days** (splitting of the embryonic disk), the twins are **monochorionic, monoamnionic.** There is only one placenta and one sac. Specific additional risks are twin–twin transfusion but particularly **umbilical cord entanglement** which can result in fetal death. This is the highest risk of all monozygotic twins.
- **After 12 days**, conjoined twins result. Most often this condition is **lethal**.

Table I-8-2. Postconception Days to Identical Twin Cleavage

Dichorionic–diamnionic	0–3 days Morula
Monochorionic–diamnionic	4–8 days Blastocyst
Monochorionic–monoamnionic	9–12 days Embryonic disk
Conjoined	>12 days Embryo

With multiple gestation, **hyperemesis gravidarum** is common due to high levels of β-hCG. Uterus is larger than dates. Maternal serum **α-fetoprotein** is excessively higher than with one fetus.

Management.

- **Antepartum:** Give mother iron and folate supplementation to prevent anemia, monitor BP to detect preeclampsia, educate mother regarding preterm labor symptoms and signs, and perform serial ultrasound examinations looking for twin–twin transfusion (amniotic fluid discordance).

- **Intrapartum:** Route of delivery is based on presentation in labor—vaginal delivery if both are cephalic presentation (50%); cesarean delivery if first twin in noncephalic presentation; route of delivery is controversial if first twin is cephalic and second twin is noncephalic.
- **Postpartum:** Watch for postpartum hemorrhage from uterine atony owing to an overdistended uterus.

ALLOIMMUNIZATION

A 32-year-old woman, G2 P1, is seen for her first prenatal visit at 12 weeks' gestation. Prenatal lab panel reveals a blood type of O negative. Atypical antibody screen (indirect Coombs test) is positive. She has been married to the same husband for 10 years and states he is the father of both her pregnancies. She did not receive RhoGAM during her last pregnancy.

With alloimmunization, a pregnant woman develops **antibodies to foreign red blood cells** (RBCs), most commonly against those of her current or previous fetus(es). It is rarely caused by transfusion of mismatched blood.

The most common RBC antigens are of the Rh system (C, c, D, E, e) (**most common is big D).**

- Antibodies to RBC antigens are detected by **indirect Coombs test** (atypical antibody test [AAT]). The concentration of antibodies is reported in dilutional titers with the lowest level being 1:1, and titers increasing by doubling (e.g., 1:1, 1:2, 1:4, 1:8, 1:16, 1:32…1:1,024, etc.).
- **Hemolytic disease of the newborn** (HDN) is a continuum ranging from hyperbilirubinemia to erythroblastosis fetalis. HDN is caused by maternal antibodies crossing into the fetal circulation and targeting antigen-positive fetal RBCs, resulting in hemolysis. When severe, this can result in anemia, fetal hydrops, and even death.

Risk Factors. Alloimmunization most commonly occurs when **fetal RBCs enter** the mother's circulation transplacentally at delivery. It can also occur if a woman is transfused with mismatched RBCs. Other pregnancy-related risk factors are amniocentesis, ectopic pregnancy, D&C, abruptio placentae, and placenta previa.

Protective Factors. ABO incompatibility decreases the risk of maternal alloimmunization from foreign RBCs. Naturally occurring anti-A and anti-B antibodies rapidly lyse foreign RBCs before maternal lymphocytes are stimulated to produce active antibodies.

Requirements (all must be present).

- Mother must be antigen-negative.
- Fetus must be antigen-positive, which means the father of the pregnancy must also be antigen-positive.
- Adequate fetal RBCs must cross over into the maternal circulation to stimulate her lymphocytes to produce antibodies to the fetal RBC antigens.
- Antibodies must be associated with HDN.
- Significant titer of maternal antibodies must be present to cross over into the fetal circulation and lead to fetal RBC hemolysis.

Management.

(1) Determine if the fetus is at risk for anemia.

- **Fetal risk is present** only if (a) atypical antibodies are detected in the mother's circulation, (b) antibodies are associated with HDN, (c) antibodies are present at a significant titer (>1:8), and (d) the father of the baby (FOB) is RBC antigen-positive.
- **No fetal risk is present** if (a) the AAT is negative, (b) antibodies are present but are NOT associated with HDN, (c) antibody titer is ≤1:8, or (d) the FOB is RBC antigen-negative.
- **If the atypical antibody titer** is ≤1:8, management is conservative. Repeat the titer monthly as long as it remains ≤1:8.

(2) **Assess if the fetus is anemic using Doppler ultrasound.** Doppler ultrasound measures peak flow velocity of blood through the fetal middle cerebral artery (MCA). As fetal anemia worsens, the peak systolic velocity rises. Doppler MCA ultrasound is the **procedure of choice** since it is **non-invasive and has a high correlation with fetal anemia.**

(3) Intervene if the **anemia is severe.** This is diagnosed when amniotic fluid bilirubin is in Liley zone III or PUBS shows fetal hematocrit to be ≤25% or MCA flow is elevated. If gestational age <34 weeks, perform intrauterine intravascular transfusion. If gestational age ≥34 weeks, perform delivery.

Prevention. RhoGAM is pooled anti-D IgG passive antibodies that are given IM to a pregnant woman when there is significant risk of fetal RBCs passing into her circulation. The passive IgG antibodies attach to the foreign RBC antigens, causing lysis to occur before the maternal lymphocytes become stimulated.

- **RhoGAM** is routinely given to Rh(D)-negative mothers at 28 weeks, and within 72 h of chorionic villus sampling (CVS), amniocentesis, or D&C. It is also given within 72 h of delivery of an Rh(D)-positive infant. About 300 mcg of RhoGAM will neutralize 15 ml of fetal RBCs or 30 mL of fetal whole blood.
- **Rosette test** is a qualitative screening test for detecting significant feto-maternal hemorrhage (≥10 mL).
- **Kleihauer-Betke test** quantitates the volume of fetal RBCs in the maternal circulation by differential staining of fetal and maternal RBCs on a peripheral smear. This can assess whether more than one vial of RhoGAM needs to be given when large volumes of fetal–maternal bleed may occur (e.g., abruptio placentae).

PRETERM LABOR

A 24-year-old woman, G2 P1, at 28 weeks' gestation by dates comes to the birthing unit complaining of regular uterine contractions every 7–10 min. She is a smoker with chronic hypertension. She has had no prenatal care. On examination her fundal height is 35 cm. Her previous pregnancy ended with spontaneous vaginal delivery at 30 weeks' gestation.

Preterm delivery is the most common cause of perinatal morbidity and mortality. Overall, 12% of pregnancies deliver prematurely. Many patients will have preterm contractions but not be in preterm labor.

Note

Fetal blood type may be determined by amniocentesis or percutaneous umbilical blood sampling (PUBS). If the fetus is RBC antigen-negative, there is no fetal risk.

OB Triad

Preterm Contractions

- Pregnancy 20–36 weeks
- ≥3 contractions in 30 min
- Dilated <2 cm and no change

OB Triad

Magnesium Toxicity

- Preterm labor tocolysis
- Respiratory depression
- Muscle weakness

OB Triad

Preterm Labor

- Pregnancy 20–36 weeks
- ≥3 contractions in 30 min
- Dilated ≥2 cm or changing

Preterm delivery **categories** include:

- **Extreme** preterm: <28 weeks
- **Very** preterm: <32 weeks
- **Moderate** preterm: 32–33 6/7 weeks
- **Late** preterm: 34–36 6/7 weeks

Risk Factors.

- **Most common:** prior preterm birth (PTB), short transvaginal (TV) cervical length (<25 mm), PROM, multiple gestation, uterine anomaly
- Others: low maternal pre-pregnancy weight, smoking, substance abuse, and short inter-pregnancy interval (<18 months)

Hazards of PTB include neonatal death, respiratory distress syndrome (RDS), patent ductus arteriosus (PDA), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD), and cerebral palsy (CP).

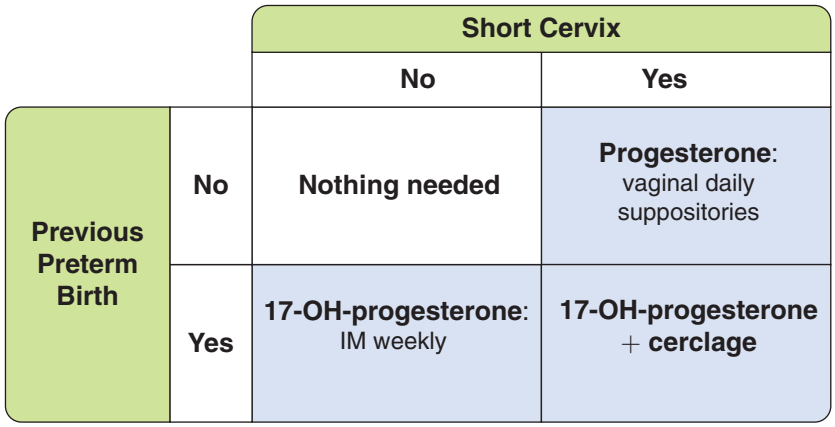

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Figure I-8-3. Risk Factors and Interventions to Prevent Preterm Birth

Prevention of Preterm Birth

High-Yield

All pregnant women should be screened for history of previous PTB on first prenatal visit and cervical length by sonogram prior to 24 weeks.

Interventions to prevent preterm delivery include the following:

- If cervical length >25 mm with prior spontaneous PTB: weekly IM 17-hydroxy progesterone caproate (17-0H-P)
- If cervical length <25 mm before 24 weeks with prior PTB: weekly IM 17-OH-P plus cervical cerclage placement
- If cervical length <20 mm before 24 weeks but no prior PTB: daily vaginal progesterone

No interventions are shown to have any benefit in cases of twin pregnancy.

Diagnosis of Preterm Labor

High-Yield

Symptoms of preterm labor include lower abdominal pain/pressure, lower back pain, increased vaginal discharge, or bloody show. Particularly in primigravidas, symptoms may be present for a number of hours to days but are not recognized as contractions by the patient.

Criteria that need to be met to make a diagnosis include:

- **Gestational age:** >20 weeks but <37 weeks
- **Uterine contractions:** at least 3 contractions in 30 minutes
- **Cervical exam:** serial examinations show a change in dilation or effacement, or a single examination shows cervical dilation >2 cm

Fetal fibronectin (fFN) is a protein matrix produced by fetal cells which acts as a biological glue, binding the trophoblast to the maternal decidua. It "leaks" into the vagina if PTB is likely and can be measured with a rapid test using a vaginal swab.

- Prerequisites for testing: gestation 22–35 weeks, cervical dilation <3 cm, and membranes intact
- Interpretation: main value of test is a negative, since chance of PTB in the next 2 weeks is <1%; with a positive result, likelihood of PTB is 50%

There are conditions under which stopping labor is either dangerous for the mother and baby or futile (makes no difference in outcome). Examples include the following:

- **Obstetric:** severe abruptio placentae, ruptured membranes, chorioamnionitis
- **Fetal:** lethal anomaly (anencephaly, renal agenesis), fetal demise or jeopardy (repetitive late decelerations)
- **Maternal:** eclampsia, severe preeclampsia, advanced cervical dilation

Interventions to Decrease Perinatal M&M

High-Yield

- **Intravenous magnesium sulfate for fetal neuroprotection:** Maternal IV $MgSO_4$ may reduce the severity and risk of cerebral palsy in surviving very preterm neonates.
  - Start infusion if PTB is anticipated <32 weeks gestation regardless of anticipated route of delivery.
  - It takes 4 hours of infusion to achieve steady state of Mg in the fetus.
- **Antenatal corticosteroid therapy for stimulation of pulmonary surfactant:** A single course of corticosteroids is recommended for pregnant women with gestational age 23–34 weeks of gestation who are at risk of preterm delivery within 7 days. Use in pregnancies 34–37 weeks is controversial.
  - A complete course is either 2 IM 12 mg doses of betamethasone given 24 hours apart or 4 IM 6 mg doses of dexamethasone given 12 hours apart.
  - Neonates whose mothers receive antenatal corticosteroids have significantly lower severity, frequency, or both of respiratory distress syndrome, intracranial hemorrhage, necrotizing enterocolitis and death.

- **Tocolytic agents.** Parenteral agents may prolong pregnancy, but for no more than 72 h. This does provide a window of time for (1) administration of maternal IM betamethasone to enhance fetal pulmonary surfactant and (2) transportation of mother and fetus in utero to a facility with neonatal intensive care. Oral tocolytic agents are no more effective than placebo.
  - **Magnesium sulfate** is a competitive inhibitor of calcium. Clinical monitoring is based on decreasing but maintaining detectable deep tendon reflexes. Side effects include muscle weakness, respiratory depression, and pulmonary edema. Magnesium overdose is treated with IV calcium gluconate. Contraindications include renal insufficiency and myasthenia gravis.
  - **β-adrenergic agonists** (e.g., terbutaline). Tocolytic effect depends on the β2-adrenergic receptor myometrial activity. Side effects include hypertension, tachycardia, and possible hyperglycemia, hypokalemia, and pulmonary edema. Contraindications include cardiac disease, diabetes mellitus, uncontrolled hyperthyroidism.
  - **Calcium-channel blockers** (e.g., nifedipine) decrease intracellular calcium. Side effects include tachycardia, hypotension, and myocardial depression. Contraindications include hypotension.
  - **Prostaglandin synthetase inhibitors** (e.g., indomethacin) decrease smooth muscle contractility by decreasing prostaglandin production. Side effects include oligohydramnios, in utero ductus arteriosus closure, and neonatal necrotizing enterocolitis. Contraindications include gestational age ≥32 weeks.

OB Triad

Beta Agonists

- Preterm labor tocolysis
- Hypokalemia
- Hyperglycemia

OB Triad

Calcium Channel Blocker

- Preterm labor tocolysis
- Hypotension
- Myocardial depression

Management of Preterm Labor

High-Yield

Management of preterm labor involves several steps.

Step 1: Confirm labor using the three criteria listed earlier—gestational age, contraction frequency, cervical exam.

Step 2: Rule out contraindications to tocolysis. Do not try to prolong pregnancy if obstetric, fetal, maternal complications are present.

Step 3: Start IV $MgSO_4$ if <32 weeks for fetal neuroprotection of cerebral palsy. Administer at least four hours before anticipated birth.

Step 4: Administer IM betamethasone if <34 weeks to stimulate fetal type II pneumocyte surfactant production. A 48-hr course is needed for full effect to take place.

Step 5: Start tocolytic therapy if <34 weeks to prolong pregnancy to allow for antenatal steroid effect. There is no benefit exceeding 48 hours. **$MgSO_4$, terbutaline**, or **nifedipine** can be used up to 34 weeks. **Indomethacin** should not be used after 32 weeks due to concerns regarding in-utero closure of the PDA.

Step 6: Start IV penicillin G if <36 weeks for GBS sepsis prophylaxis (use vancomycin if allergic to penicillin G). First obtain recto-vaginal cultures.

OB Triad

Indomethacin

- Preterm labor tocolysis
- Oligohydramnios
- PDA closure in utero

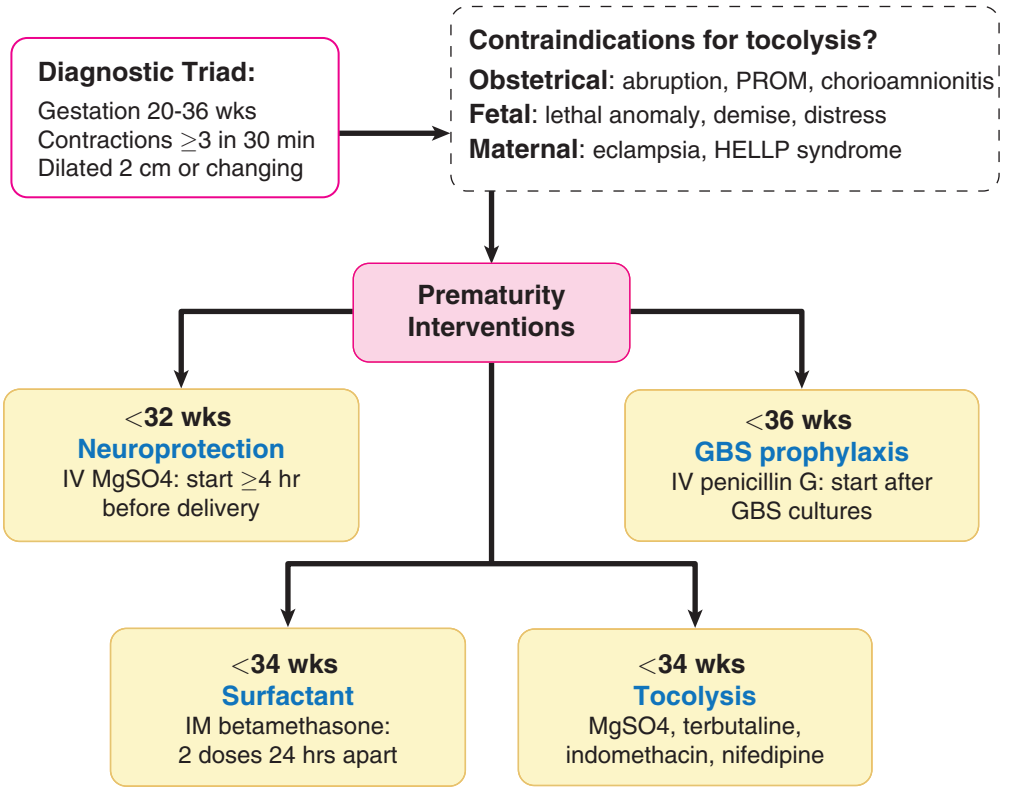

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Figure I-8-4. Diagnosis and Management for Preterm Birth

PREMATURE RUPTURE OF MEMBRANES

A 22-year-old primigravida at 33 weeks' gestation comes to the birthing unit stating that 2 h ago she had a gush of fluid from her vagina. She denies vaginal bleeding or uterine contractions. Her perineum appears moist to gross inspection. On examination her temperature is 38.9 C (102 F).

OB Triad

Ruptured Membranes

- Posterior fornix **pooling**
- Fluid is nitrazine (phenaphthazine) (+)
- Glass slide drying: fern (+)

Premature rupture of membranes (PROM) is rupture of the fetal membranes before the onset of labor, whether at term or preterm.

Risk Factors. Ascending infection from the lower genital tract is the most common risk factor for PROM. Other risk factors are local membrane defects and cigarette smoking.

Clinical Presentation. Typical history is a sudden gush of copious vaginal fluid. On external examination, clear fluid is flowing out of the vagina. Oligohydramnios is seen on ultrasound examination.

Diagnosis is made by **sterile speculum examination** meeting the following criteria:

- **Pooling positive:** clear, watery amniotic fluid is seen in the posterior vaginal fornix
- **Nitrazine positive:** the fluid turns pH-sensitive paper blue
- **Fern positive:** the fluid displays a ferning pattern when allowed to air dry on a microscope glass slide

Chorioamnionitis is diagnosed **clinically** with the following criteria: maternal fever plus uterine tenderness in the presence of confirmed PROM in the absence of a URI or UTI.

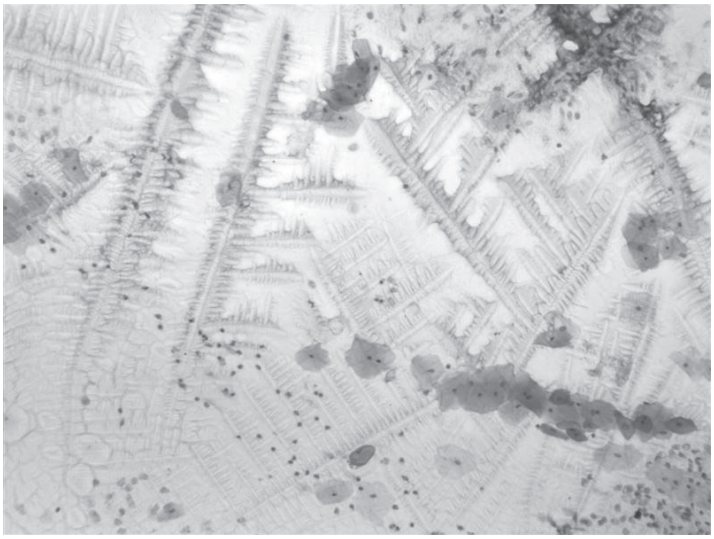

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Figure I-8-5. Ferning Pattern of Amniotic Fluid

Management.

- If **uterine contractions** occur, tocolysis is contraindicated.
- If **chorioamnionitis** is present, obtain cervical cultures, start broad-spectrum therapeutic IV antibiotics, and initiate prompt delivery.
- If **no infection** is present, management will be based on gestational age as follows:
  - **Before viability** (<23 weeks), outcome is dismal. Either induce labor or manage patient with bed rest at home. Risk of fetal pulmonary hypoplasia is high.
  - **With preterm viability** (23 0/7–33 6/7 weeks), conservative management. Hospitalize the patient at bed rest, administer IM betamethasone to enhance fetal lung maturity if <34 weeks, obtain cervical cultures, and start a 7-day course of prophylactic ampicillin and erythromycin.
  - **At term** (≥34 weeks), initiate prompt delivery. If vaginal delivery is expected, use oxytocin or prostaglandins as indicated. Otherwise, perform cesarean delivery.

OB Triad

Chorioamnionitis

- Ruptured membranes
- Maternal fever
- No UTI or URI

Table I-8-3. Hazards Associated with PROM

If Fetus Remains In Utero	If Preterm Delivery Occurs
Neonatal conditions • Infection and sepsis • Deformations • Umbilical cord compression • Pulmonary hypoplasia	**Neonatal conditions** • Respiratory distress syndrome (most common) • Patent ductus arteriosus • Intraventricular hemorrhage • Necrotizing enterocolitis • Retinopathy of prematurity • Bronchopulmonary dysplasia • Cerebral palsy
Maternal conditions • Chorioamnionitis, sepsis • Deep venous thrombosis (DVT) • Psychosocial separation	

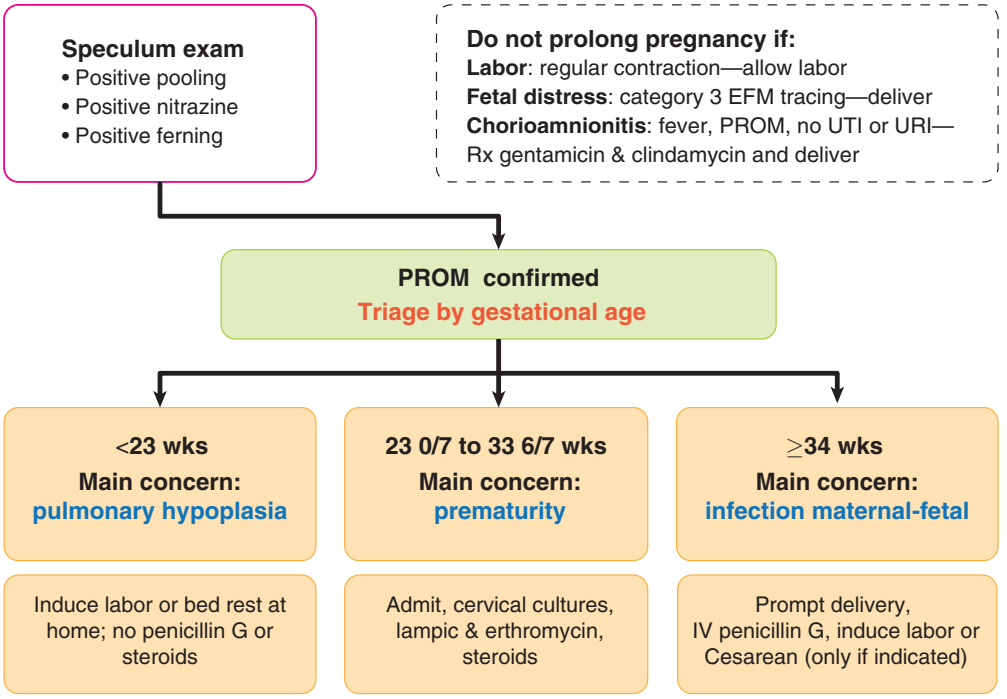

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Figure I-8-6. Diagnosis and Management for Premature Rupture Membranes

POST-TERM PREGNANCY

A 21-year-old primigravida at 42 weeks' gestation by dates comes to the outpatient prenatal clinic. She has been seen for prenatal care since 12 weeks' gestation, confirmed by an early sonogram. She states that fetal movements have been decreasing. Fundal height measurement is 42 cm. Her cervix is long, closed, posterior, and firm. Nonstress test is reactive, but amniotic fluid index is 4 cm.

The most precise definition of post-term pregnancy is pregnancy that continues for ≥40 weeks or ≥280 days postconception (6% of all pregnancies). Because the date of conception is infrequently known, a practical definition is **pregnancy that continues ≥42 weeks** or **≥294 days after the first day of the last menstrual period**.

- Generally, 50% of patients deliver by 40 weeks, 75% by 41 weeks, and 90% by 42 weeks.
- These statistics assume ovulation occurred on day 14 of a 28-day menstrual cycle (because up to 50% of patients have cycles longer than 28 days, these numbers are probably overstated).

The most common cause of true postdates cases are idiopathic (no known cause). It does occur more commonly in young primigravidas and rarely with placental sulfatase deficiency. Pregnancies with anencephalic fetuses are the longest pregnancies reported.

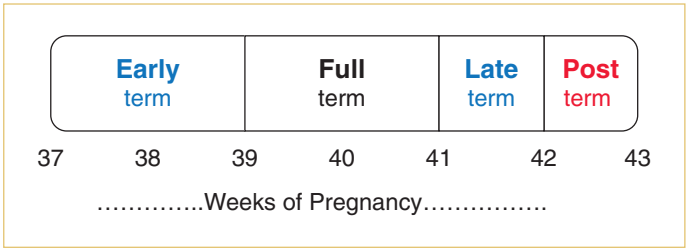

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Figure I-8-7. Four Categories of Term Pregnancy

With post-term pregnancy, perinatal mortality is increased two- to threefold. This is a direct result of changes on placental function over time.

- **Macrosomia syndrome.** In most patients, **placental function continues** providing nutritional substrates and gas exchange to the fetus, resulting in a healthy but large fetus. **Cesarean rate is increased** owing to prolonged or arrested labor. Shoulder dystocia is more common with risks of fetal hypoxemia and brachial plexus injury.
- **Dysmaturity syndrome.** In a minority of patients, **placental function declines** as infarction and aging leads to placental scarring and loss of subcutaneous tissue. This reduction of metabolic and respiratory support to the fetus can lead to the asphyxia that is responsible for the increased perinatal morbidity and mortality. **Cesarean rate is increased** owing to nonreassuring fetal heart rate patterns. Oligohydramnios results in umbilical cord compression. Hypoxia results in acidosis and in utero meconium passage.

Management is based on two factors.

- **Confidence in dates.** Identify how much confidence can be placed on the gestational age being truly >42 weeks.
- **Favorableness of the cervix.** Assess the likelihood of successful induction of labor by assessing cervical dilation, effacement, position, consistency, and station. The **Bishop score** is a numerical expression of how favorable the cervix is and the likelihood of successful labor induction.

- A **favorable or ripe cervix** is dilated, effaced, soft, and anterior. A Bishop score ≥6 is an accurate predictor of successful vaginal delivery with induction of labor.
- An **unfavorable cervix** is closed, uneffaced, firm, and posterior. A Bishop score <3 is a predictor of unsuccessful vaginal delivery with induction of labor.

Table I-8-4. Bishop Scoring Method

Parameter\Score	0	1	2	3
Position	Posterior	Intermediate	Anterior	–
Consistency	Firm	Intermediate	Soft	–
Effacement	0–30%	31–50%	51–80%	>80%
Dilation	0 cm	1–2 cm	3–4 cm	>5 cm
Fetal station	−3	−2	−1, 0	+1,+2

Patients can be classified into 3 groups.

- **Dates sure, favorable cervix.** Management is aggressive. There is no benefit to the fetus or mother in continuing the pregnancy. Induce labor with IV oxytocin and artificial rupture of membranes.
- **Dates sure, unfavorable cervix.** Management is controversial. Management could be aggressive, with mechanical cervical ripening using a Foley balloon catheter placed through the cervical canal, or with oral/vaginal/cervical prostaglandin to soften the cervix. Either method is followed by IV oxytocin.
- **Dates unsure.** Management is conservative. Perform twice weekly NSTs and AFIs to ensure fetal well-being and await spontaneous labor. If fetal jeopardy is identified, delivery should be expedited.

Table I-8-5. Placental Function in Post-Term Pregnancy

Maintained	Deteriorates
Macrosomia (80%)	Dysmaturity (20%)
Difficult labor and delivery	Placental insufficiency
↑ C section (forceps, vacuum extractor, shoulder dystocia, birth trauma)	↑ C section (acidosis, meconium aspiration, oxygen deprivation)

Prevention of **meconium aspiration syndrome** (MAS). Current recommendations reflect the understanding that MAS has its origin in-utero, often prior to labor. Randomized studies have shown that most interventions in the neonatal period do not lead to a change in the perinatal outcome.

- Amnioinfusion can be helpful to prevent umbilical cord compression but makes no difference in preventing MAS; **do not routinely perform**.
- Suctioning of fetal nose and pharynx makes no difference in preventing MAS; **do not routinely perform**.
- Laryngoscopic visualization of vocal cords is indicated only if the neonate is depressed; **perform selectively**.

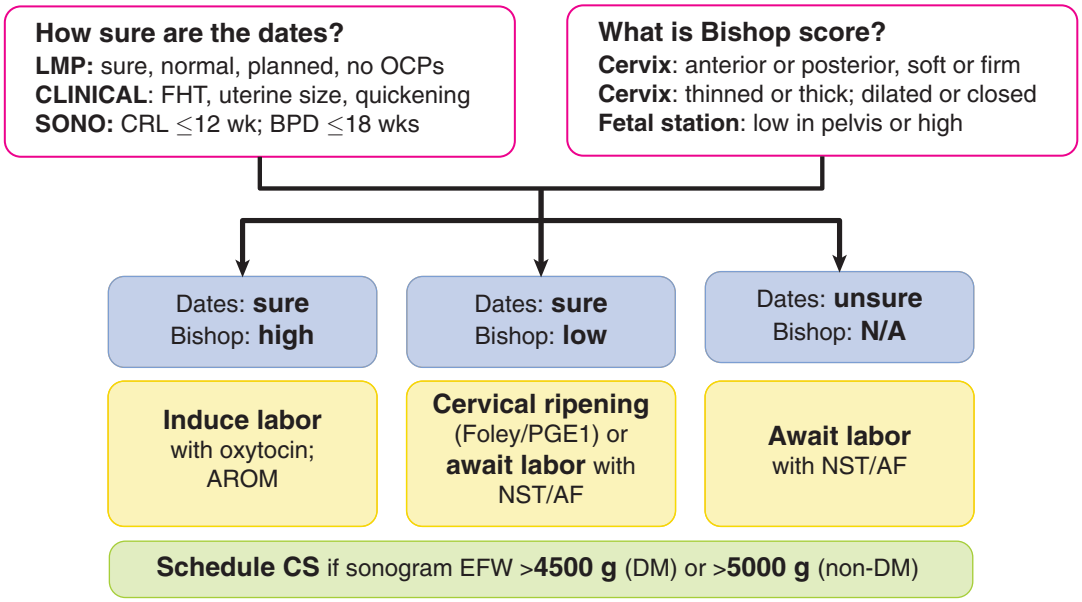

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Figure I-8-8. Diagnosis and Management for Post-Dates Pregnancy

Hypertensive Complications 9

Learning Objectives

- ❑ Differentiate between gestational hypertension, preeclampsia, eclampsia, and chronic hypertension with or without superimposed preeclampsia
- ❑ Describe the diagnosis, management, and complications of hypertensive syndromes in pregnancy
- ❑ Answer questions about HELLP syndrome

HYPERTENSION IN PREGNANCY

Systolic and diastolic BP both decline early in the first trimester, reaching a nadir by 24–28 weeks; then they gradually rise toward term but never return quite to prepregnancy baseline.

- Diastolic falls more than systolic, as much as 15 mm Hg.
- **Arterial BP is never normally elevated in pregnancy**.

GESTATIONAL HYPERTENSION

A 19-year-old primigravida is seen in the outpatient prenatal clinic for routine visit. She is at 32 weeks' gestation, confirmed by first trimester sonogram. She has no complaints. She denies headache, epigastric pain, or visual disturbances. She has gained 2 pounds since her last visit two weeks ago. On examination her blood pressure is 155/95 mm Hg, which is persistent on repeat check 10 minutes later. She has only trace pedal edema. A spot urine dipstick is negative.

Gestational hypertension is diagnosed with **sustained** elevation of BP ≥140/90 mm Hg after 20 weeks of pregnancy **without** proteinuria. BP returns to normal baseline postpartum.

No symptoms of preeclampsia are seen, e.g., headache, epigastric pain, visual disturbances. Physical findings are unremarkable for pregnancy. **Lab tests are unremarkable for pregnancy**. Proteinuria is absent.

Preeclampsia should always be ruled out.

Diagnosis is made with sustained elevation of BP >140/90 mm Hg without proteinuria (key finding).

OB Triad

Gestational Hypertension

- Pregnancy >20 wk
- Sustained HTN
- No proteinuria

Management. Conservative outpatient management with close observation since 30% of patients will develop preeclampsia. Appropriate lab testing should be performed to rule out preeclampsia, e.g., urine protein, hemoconcentration assessment. Deliver at 37 weeks.

OB Triad

Preeclampsia

- Pregnancy >20 wk
- Sustained HTN (>140/90 mm Hg)
- Proteinuria (≥300 mg/24 h)

PREECLAMPSIA

A 21-year-old primigravida without severe features is seen in the outpatient prenatal clinic for routine visit. She is at 32 weeks' gestation, confirmed by first trimester sonogram. She denies headache, epigastric pain, or visual disturbances. She has gained 10 pounds since her last visit two weeks ago. On examination her BP is 155/95 mm Hg and it remains unchanged on repeat check in 15 min. She has 2+ pedal edema, and her fingers appear swollen. A spot urine dipstick shows 2+ protein.

Preeclampsia is **sustained BP** elevation in pregnancy **after 20 weeks'** gestation in the absence of preexisting hypertension.

Pathophysiology involves **diffuse vasospasm** caused by (1) loss of the normal pregnancy-related refractoriness to vasoactive substances such as angiotensin and (2) relative or absolute changes in the following **prostaglandin** substances:

- Increases in the vasoconstrictor thromboxane
- Decreases in the potent vasodilator **prostacyclin**

This vasospasm contributes to intravascular volume constriction and decreased perfusion of most organs including uteroplacental unit, kidneys, liver, brain, and heart. Decreased renal blood flow leads to decreased clearance of body metabolic wastes. Capillary injury leads to loss of intravascular volume into the interstitial space and subsequent edema.

In preeclampsia *without* severe features, the symptoms and physical findings (if present) are generally related to excess weight gain and fluid retention. The presence of new onset of persistent headache, epigastric pain, or visual disturbances would move the diagnosis from preeclampsia without severe features to preeclampsia *with* severe features.

Differential Diagnosis. Chronic hypertension should always be ruled out.

Diagnosis is made with the **diagnostic dyad**, as there are no pathognomic tests:

- **Sustained BP elevation** of ≥140/90 mm Hg
- **Proteinuria** of ≥300 mg on a 24 h urine collection or protein/creatinine ratio of ≥0.3

Risk Factors. Preeclampsia is found 8 times more frequently in **primiparas**. Other risk factors are multiple gestation, hydatidiform mole, diabetes mellitus, age extremes, chronic hypertension, and chronic renal disease.

Lab abnormalities include the following: Evidence of **hemoconcentration** is shown by elevation of hemoglobin, hematocrit, blood urea nitrogen (BUN), serum creatinine, and serum uric acid. **Proteinuria** is present (described under diagnostic criteria). Evidence of disseminated intravascular coagulation **(DIC)** or liver enzyme elevation would move the diagnosis from preeclampsia without severe features to preeclampsia with severe features.

Management. The only definitive cure is delivery and removal of all fetal-placental tissue. However, delivery may be deferred in preeclampsia without severe features to minimize neonatal complications of prematurity. Management is based on gestational age.

- **Conservative management.** Before 37 weeks' gestation as long as mother and fetus are stable, mild preeclampsia is managed in the hospital or as outpatient, watching for possible progression to severe preeclampsia. No antihypertensive agents or $MgSO_4$ are used.
- **Delivery.** At ≥37 weeks' gestation, delivery is indicated with dilute IV oxytocin induction of labor and continuous infusion of IV $MgSO_4$ to prevent eclamptic seizures.

Complications can include progression from preeclampsia without severe features to preeclampsia with severe features.

PREECLAMPSIA WITH SEVERE FEATURES

> A 21-year-old primigravida is seen in the outpatient prenatal clinic for a routine visit. She is at 32 weeks' gestation, confirmed by first trimester sonogram. For the past 24 h she had experienced severe, unremitting occipital headache and mid-epigastric pain not relieved by acetaminophen, and she has also seen light flashes and spots in her vision. She has gained 10 pounds since her last visit two weeks ago. On examination her BP is 165/115 mm Hg. She has 2+ pedal edema, and her fingers appear swollen. Fundal height is 29 cm. Fetal heart tones are regular at 145 beats/min. A spot urine dipstick shows 4+ protein.

The pathophysiology of preeclampsia with severe features is the same as preeclampsia, but involves **severe diffuse vasospasm** and **more intense capillary injury** to where the ischemia demonstrates itself in overt, usually multiorgan system injury. Characteristic presenting symptoms include presence of new onset of persistent headache, epigastric pain, or visual disturbances.

Diagnosis is made in the presence of (at least) mild elevation of BP and mild proteinuria plus any one of the following:

- **Sustained BP** elevation of ≥160/110
- **Evidence of maternal jeopardy:** may include symptoms (headache, epigastric pain, visual changes), thrombocytopenia (platelet count <100,000/mL), doubling of liver transaminases, pulmonary edema, serum creatinine >1.1 mg/dL, or doubling of serum creatinine
- Possible **edema**

Risk factors are the same as preeclampsia, with the addition of diseases with small vessel disease such as systemic lupus and longstanding overt diabetes.

Lab abnormalities include the following: Evidence of **hemoconcentration** will be more severe. Proteinuria is described under diagnostic tests. Evidence of DIC and hepatocellular injury is characteristic of severe preeclampsia.

Note

Preeclampsia with severe features has many presentations.

Note

Quantification of proteinuria (e.g., ≥5 g on a 24 h urine collection) is no longer used as a finding indicating a severe feature of preeclampsia. Proteinuria may even be absent, yet the diagnosis still can be made if there is new onset of hypertension with evidence of maternal jeopardy.

OB Triad

Preeclampsia with Severe Features

- Pregnancy >20 wk
- Sustained HTN (>140/90 mm Hg)
- Headache or epigastric pain or visual changes
- Pregnancy >20 wk
- Sustained HTN (>140/90 mm Hg)
- DIC or ↑ liver enzymes or pulmonary edema

Note

Because IUGR is managed similarly with and without preeclampsia, it has been removed as a finding indicating a severe feature of preeclampsia.

Management. Aggressive prompt delivery is indicated for preeclampsia with severe features at any gestational age with evidence of maternal jeopardy or fetal jeopardy. Main goals are seizure prevention and BP control.

- **Administer IV $MgSO_4$** to prevent convulsions. Give a 5 g loading dose, then continue maintenance infusion of 2 g/h. Continue IV $MgSO_4$ for 24 hours after delivery.
- **Lower BP** to diastolic values 90–100 mm Hg with IV hydralazine and/or labetalol. More aggressive BP control may jeopardize uteroplacental fetal perfusion.
- **Attempt vaginal delivery** with IV oxytocin infusion if mother and fetus are stable.
- Cesarean section is only for obstetric indications.

Conservative inpatient management may rarely be attempted in absence of maternal and fetal jeopardy with gestational age 26–34 weeks if BP can be brought <160/110 mm Hg. This should take place in an intensive care, tertiary-care setting. Continuous IV $MgSO_4$ should be administered, and maternal betamethasone should be given to enhance fetal lung maturity.

Complications can include progression from preeclampsia with severe features to eclampsia.

ECLAMPSIA

> A 21-year-old primigravida is brought to the emergency department after suffering from a generalized tonic-clonic seizure at 32 weeks' gestation. The seizure was preceded by a severe headache. She lost control of her bowels and bladder. She has gained 10 pounds since her last prenatal visit two weeks ago. On examination she is unresponsive and in a postictal state. BP is 185/115 mm Hg and spot urine dipstick shows 4+ protein.

Eclampsia is the presence of **unexplained generalized seizures** in a hypertensive, proteinuric pregnant woman in the last half of pregnancy. Pathophysiology is **severe diffuse cerebral vasospasm** resulting in cerebral perfusion deficits and cerebral edema.

In addition to those presenting symptoms of mild and severe preeclampsia, the most significant finding is **unexplained tonic-clonic seizures**.

Lab abnormalities are the same as those found with mild and severe preeclampsia.

Diagnosis is made clinically with unexplained generalized seizures occurring in a hypertensive, proteinuric pregnant woman in the last half of pregnancy.

Risk factors are the same as in preeclampsia. A primary seizure disorder does not predispose to eclampsia.

Management. The first step is to protect the mother's airway and tongue.

- **Administer $MgSO_4$** with an IV bolus of 5 g to stop seizures, continuing maintenance infusion rate of 2 g/h. Continue IV $MgSO_4$ for 24 hours after delivery.
- **Aggressive prompt delivery** is indicated for eclampsia at any gestational age after stabilization of the mother and the fetus. Attempt vaginal delivery with IV oxytocin infusion if mother and fetus are stable.
- **Lower diastolic BP** between 90–100 mm Hg with IV hydralazine and/or labetalol.

Complications can include intracerebral hemorrhage, with possible death.

Table I-9-1. Preeclampsia–Eclampsia Spectrum

	Preeclampsia without Severe Features	Preeclampsia with Severe Features	Eclampsia
Symptoms	None	Headache or epigastric pain or visual changes	Unexplained convulsions
Sustained ↑ blood pressure	>140/90 mm Hg <160/110 mm Hg	At least >140/90 mm Hg (if other findings) or >160/110 mm Hg	At least >140/90 mm Hg
Laboratory tests	Hemoconcentration >300 mg proteinuria in 24 hrs No DIC, normal liver function tests	Hemoconcentration, or DIC, or ↑ liver function tests	Hemoconcentration At least 1-2 + proteinuria
Other findings	None	Pulmonary edema	May or may not be present
Management	<36 wk: observe in hospital, no $MgSO_4$, or blood pressure meds ≥36 wks: prompt delivery	$MgSO_4$: prevent or treat convulsions Lower diastolic, BP to 90–100 mm Hg Prompt delivery: not necessarily Cesarean section	

CHRONIC HYPERTENSION WITH OR WITHOUT SUPERIMPOSED PREECLAMPSIA

A 35-year-old multigravida is seen in the outpatient prenatal clinic for her first prenatal visit. She is at 12 weeks' gestation with a BP of 155/95 mm Hg. Chronic hypertension was diagnosed five years ago for which she has been treated with oral nifedipine. A spot urine dipstick protein is 2+. A recent 24 h urine collection showed 1.2 g of protein and a creatinine clearance of 85 ml/min. Serum creatinine is 1.2 mg/dl. She has no complaints of headache or visual changes.

Pathophysiology is **vasospasm** causing **decreased end-organ perfusion**, resulting in injury and damage. The acute problems arise from excessive systolic pressures, whereas the long-term problems arise from excessive diastolic pressures. **Diagnosis** of chronic HTN is made when BP ≥140/90 mm Hg with onset before the pregnancy or before 20 weeks' gestation.

Risk Factors. Most chronic hypertension (HTN) is **idiopathic** without specific antecedents. Risk factors are obesity, advanced maternal age, positive family history, renal disease, diabetes, and systemic lupus erythematosus.

OB Triad

Chronic HTN

- Pregnancy <20 wk or prepregnancy
- Sustained HTN (>140/90 mm Hg)
- +/– proteinuria

Pregnancy prognosis with **chronic HTN** is as follows:

- **Good:** Favorable maternal and neonatal outcome is found when BP 140/90–179/109 mm Hg and no evidence of end-organ damage.
- **Poor:** Pregnancy complications are more common in patients with severe HTN with the following end-organ damage: cardiac, renal, and retinal.
  - **Renal disease:** pregnancy loss rates increase significantly if serum creatinine value >1.4 mg/dL
  - **Retinopathy:** longstanding HTN is associated with retinal vascular changes including hemorrhages, exudates, and narrowing
  - **Left ventricular hypertrophy:** seen mostly in women with prolonged BP values >180/110 mm Hg
- **Worst:** Tenfold higher fetal loss rate if uncontrolled HTN (before conception or early in pregnancy) and chronic HTN with superimposed preeclampsia.

OB Triad

Chronic HTN with Superimposed Preeclampsia

- Chronic HTN
- Worsening BP
- Worsening proteinuria

Pregnancy prognosis with **chronic HTN with superimposed preeclampsia** (25% of patients with chronic HTN) is as follows:

- Risk factors include renal insufficiency, HTN for previous 4+ years, and HTN in a previous pregnancy.
- Adverse pregnancy outcomes for both mother and baby are markedly increased. Abruptio placentae incidence is markedly increased.
- Diagnosis is made on the basis of established chronic HTN along with any of the following: documented **rising BP values**, demonstrated **worsening proteinuria**, or evidence of **maternal jeopardy** (headache, epigastric pain, visual changes, thrombocytopenia [platelet count <100,000/mL], elevated liver enzymes, pulmonary edema, oliguria [<750 mL/24 h], or cyanosis). Edema may or may not be seen.

Lab abnormalities include the following:

- Mild HTN and no end-organ involvement have normal lab tests, whereas those with renal disease may have evidence of decreased renal function including proteinuria, lowered creatinine clearance, and elevated BUN, creatinine, and uric acid.
- Chronic HTN patients have a spectrum of etiologies and disease severity.

Antihypertensive drug therapy issues include the following:

- **Discontinuing medications** may be done in patients with mild-to-moderate HTN caused by the normal decrease in BP that occurs in pregnancy. Pharmacologic treatment in patients with diastolic BP <90 mm Hg or systolic BP <140 mm Hg does not improve either maternal or fetal outcome.
- **Maintaining medications** may be necessary in patients with severe HTN. The drug of choice is methyl-dopa because of extensive experience and documented fetal safety but labetalol and atenolol are acceptable alternatives. However, β-blocking agents are associated with intrauterine growth retardation (IUGR).
- **"Never use" medications:** Angiotensin-converting enzyme inhibitors are contraindicated in pregnancy, as they have been associated with fetal hypocalvaria, renal failure, oligohydramnios, and death. **Diuretics** should not be initiated during pregnancy owing to possible adverse fetal effects of associated plasma volume reduction.
- **BP target range.** Reduction of BP to normal levels in pregnancy may jeopardize uteroplacental blood flow. Maintain diastolic values between **90–100 mm Hg**.

Management. Conservative outpatient management for uncomplicated mild-to-moderate chronic HTN.

Stop drug therapy. Attempt discontinuation of antihypertensive agents. Follow guideline outlined.

- **Serial sonograms** and antenatal testing are appropriate after 30 weeks' gestation to monitor for increased risk of IUGR.
- **Serial BP and urine protein** assessment is indicated for early identification of superimposed preeclampsia.
- **Induce labor at 38 weeks**.

Aggressive prompt delivery for chronic HTN with superimposed preeclampsia at any gestational age.

- Administer IV **$MgSO_4$** to prevent convulsions. Continue IV $MgSO_4$ for 24 hours after delivery.
- **Keep diastolic BP** between 90 and 100 mm Hg with IV hydralazine and/or labetalol.
- Attempt **vaginal delivery** with IV oxytocin infusion if mother and fetus are stable.

Complications can include progression from chronic HTN to superimposed preeclampsia, which can lead to maternal and fetal death.

HELLP SYNDROME

A 32-year-old multigravida is at 32 weeks' gestation. At a routine prenatal visit her BP was noted to be 160/105 mm Hg. Previous BP readings were normal. Preeclampsia workup was begun and revealed the following: elevated total bilirubin, lactate dehydrogenase, alanine aminotransferase, and aspartate aminotransferase, as well as platelet count of 85,000. She has no complaints of headache or visual changes.

HELLP syndrome occurs in 5–10% of preeclamptic patients and is characterized by hemolysis (**H**), elevated liver enzymes (**EL**), and low platelets (**LP**). It can be confused with thrombotic thrombocytopenic purpura and hemolytic uremic syndrome. HTN, although frequently seen, is not always present.

Risk Factors. HELLP syndrome occurs two times as often in multigravidas as primigravidas.

Management. Prompt delivery at any gestational age. Use of maternal **corticosteroids** may enhance postpartum normalization of liver enzymes and platelet count. Complicating conditions associated with HELLP include DIC, abruptio placentae, fetal demise, ascites, and hepatic rupture.

OB Triad

HELLP Syndrome

- Hemolysis
- ↑ liver enzymes
- ↓ platelets

Medical Complications in Pregnancy

10

Learning Objectives

- ❏ Describe the risks and special management of concurrent medical conditions in pregnancy, including seizure disorders, DM, anemia, thyroid disease, cardiac disease, and liver disease
- ❏ Manage common infections occurring in pregnancy including urinary tract infections, pyelonephritis, cystitis, bacteriuria, and asymptomatic bacteriuria
- ❏ Give an overview of diagnosis and management of thrombophilias and antiphospholipid syndrome

CARDIAC DISEASE

A 30-year-old multigravida with a childhood history of rheumatic fever has echocardiography-diagnosed mitral stenosis. She is now at 20 weeks' gestation and has no symptoms at rest but has mild shortness of breath and dyspnea with activity. On examination she has a diastolic murmur.

Cardiac disease includes general types of heart disease.

- **Coronary heart disease** (rarely found in women of childbearing age). Adverse consequences of hypoxic heart disease include miscarriage, fetal death, preterm delivery, and increased perinatal morbidity and mortality.
- **Rheumatic heart disease** (most common **acquired lesion** in pregnancy). The most common rheumatic heart disease is mitral stenosis. With severe stenosis (mitral valve area <2 cm^2), the main problem is **inadequate diastolic flow** from the left atrium to the left ventricle. Obstruction to left ventricular filling may lead to left atrial enlargement, pulmonary congestion, atrial fibrillation, and subacute bacterial endocarditis (SBE) with valvular vegetations causing thromboemboli. Tachycardia and increased plasma volume, which are normal changes of pregnancy, will only exacerbate these problems. Treatment includes minimizing tachycardia and excessive intravascular volume. Balloon valvuloplasty may need to be performed as a last resort.
- **Congenital heart disease** (most common **congenital lesions** are atrial and ventricular septal defects [ASDs/VSDs]). The **most common cyanotic** congenital heart disease in pregnancy is tetralogy of Fallot. ASDs and VSDs are tolerated well with pregnancy, as are any regurgitation lesions.

Signs of heart disease include the following:

- Any diastolic or continuous heart murmur
- Any systolic murmur associated with a thrill
- Any severe arrhythmias
- Unequivocal cardiac enlargement

Maternal Mortality Risk

- **Low maternal mortality** (<1% risk of death): ASD, VSD, patent ductus arteriosus (PDA), minimal mitral stenosis, porcine heart valve, and corrected tetralogy of Fallot.
- **Intermediate maternal mortality** (5–15% risk of death): mitral stenosis with atrial fibrillation, artificial heart valve, uncorrected tetralogy of Fallot, and Marfan syndrome with normal aortic root diameter.
- **High maternal mortality** (25–50% risk of death): pulmonary hypertension, Eisenmenger's syndrome, Marfan syndrome with aortic root >40 mm diameter, and peripartum cardiomyopathy.

Unique High-Risk Conditions

High-Yield

- **Eisenmenger syndrome** is characterized by pulmonary hypertension and a bidirectional intra-cardiac shunt. The normal decrease in systemic vascular resistance (SVR) in pregnancy places the patient at risk for having the pulmonary vascular resistance (PVR) exceed the SVR. When this develops, the path of least resistance for blood from the right heart is to bypass the pulmonary circulation across the shunt. This results in the left heart pumping unoxygenated blood into the systemic circulation, resulting in a 50% mortality risk. Management is by avoiding hypotension.
- **Marfan syndrome** is an autosomal dominant connective tissue disorder. In pregnancy, if the aortic root diameter is >40 mm, the risk of aortic dissection is high, placing the patient at a 50% mortality risk.
- In **peripartum cardiomyopathy**, the patient has no underlying heart disease but develops idiopathic biventricular cardiac decompensation between the last few weeks of pregnancy and the first few months postpartum. Left ventricular ejection fraction is <45%. Risk factors include advanced maternal age, multiparity, hypertension, and multiple pregnancy. Mortality rate is 75% if reversal does not occur within six months. Management is supportive, in intensive care.

OB Triad

Peripartum Cardiomyopathy

- Late pregnancy or postpartum
- Multiparity
- Biventricular cardiac failure

Classification of Heart Disease in Pregnancy

High-Yield

Following are the **New York Heart Association** (NYHA) functional classifications of heart disease in pregnancy:

- **Class I:** no signs or symptoms of cardiac decompensation with physical activity
- **Class II:** no symptoms at rest, but minor limitations with activity
- **Class III:** no symptoms at rest, but marked limitations with activity
- **Class IV:** symptoms present at rest, increasing with any physical activity

Specific Management

High-Yield

- **Antepartum.** Left lateral rest, 2 g sodium diet, digitalis as indicated, diuretics as indicated, avoid strenuous activity, avoid anemia, fetal echocardiogram (if patient has congenital heart disease).

- **Intrapartum.** Aim for vaginal delivery, left lateral rest, monitor intravascular volume, administer oxygen, reassurance, sedation, SBE prophylaxis, epidural, no pushing, elective forceps to shorten the second stage of labor, possible arterial line and pulmonary artery catheter (if Class III or IV status).
- **Postpartum.** Watch closely for postpartum intravascular overload caused by sudden emptying of uterine venous sinuses after placental delivery.

Table I-10-1. Heart Disease in Pregnancy

Diagnosis	Problems	Management
Rheumatic mitral stenosis	↓ diastolic filling time	↓ HR; ↓ IV vol
ASD, VSD	Regurgitation	Conservative
Tetralogy of Fallot corrected	No problem	Conservative
Eisenmenger syndrome	Pulmonary HTN Intracardiac shunt	Avoid hypotension
Marfan syndrome	Dilated aortic root External diameter ≥4 cm	Surgical reconstruction
Peripartum cardiomyopathy	Biventricular cardiac failure	Supportive care

THYROID DISEASE

A 23-year-old primigravida is at 30 weeks' gestation. She has lost 4 pounds during the past two months. She states her heart "feels like it is racing," and her resting pulse is 135 beats/min. There is a noticeable tremor when she holds her arms out straight. Her eyes appear prominent and protruding. She is complaining of frequent uterine contractions.

In **normal thyroid physiology**, increased thyroid blood flow leads to thyromegaly. In pregnancy, increased glomerular filtration rate (GFR) enhances iodine excretion, lowering plasma iodine concentrations. Estrogen causes an increase in liver-produced thyroid binding globulin (TBG), thus increasing total T3 and T4. However, **free T3 and T4 remain unchanged**. Fetal thyroid function begins as early as 12 weeks with minimal transfer of T3 or T4 across the placenta.

Hyperthyroidism

High-Yield

The underlying etiology of hyperthyroidism may be Graves' disease, toxic nodular goiter (Plummer's disease), hydatidiform mole, or toxic diffuse goiter.

- **If uncontrolled**, it is associated with increased spontaneous abortions, prematurity, intrauterine growth retardation (IUGR), and perinatal morbidity and mortality.
- **If controlled**, pregnancy outcome is not altered. Clinical features include elevated resting pulse, thyromegaly, exophthalmos, inadequate weight gain or even weight loss, and markedly elevated total and free T_4.

OB Triad

Graves Disease

- ↓ TSH level
- ↑ free T_4 level
- TSHR-Ab

Thyroid storm is a life-threatening hypermetabolic state presenting with pyrexia, tachycardia, and severe dehydration. Management is propylthiouracil (PTU), β-blocking agents, steroids, and iodine.

Graves' disease (most common kind of hyperthyroidism in pregnancy) is mediated by autoimmune production of thyrotropin-receptor antibodies (TSHR-Ab) that drives thyroid hormone production independent of thyrotropin (TSH). TSHR-Ab can cross the placenta, potentially causing fetal hyperthyroidism.

Diagnosis. Diagnosis is confirmed by elevated free T_4 and TSHR-Ab, as well as low TSH in the presence of clinical features described above.

Management. **Antithyroid medications** are the first line of therapy in pregnancy, but they can cross the placentae leading to fetal hypothyroidism. PTU and methimazole are thioamides that block thyroid hormone synthesis. **Subtotal thyroidectomy** is primarily indicated when antithyroid medical therapy fails and is ideally performed in the second trimester.

Thyroid ablation with radioactive iodine (I^{131}) is **contraindicated** because it can cross the placentae, destroying the fetal thyroid.

Note

Methimazole is an FDA pregnancy **category D** so should not be used in the first trimester (it is acceptable in the second and third). **PTU** has a risk of liver failure (rare) so should be used only in the first trimester.

Hypothyroidism

High-Yield

Hypothyroidism is most commonly a primary thyroid defect and often results in **anovulation** and **infertility**.

- **If uncontrolled**, it is associated with spontaneous abortion; however, if pregnancy continues, the infant is healthy.
- **If controlled** with appropriate thyroid replacement, normal fertility and pregnancy outcomes are noted.

OB Triad

Hypothyroidism

- ↑ TSH level
- ↓ free T_4 level
- Anovulation

Diagnosis. Diagnosis is confirmed with an elevated TSH.

Management. Increase supplemental thyroid hormone by 30% in pregnancy.

Table I-10-2. Thyroid Disorders in Pregnancy

	Hyperthyroid	Hypothyroid
Most common cause	Graves disease	Hashimoto's thyroiditis
Diagnostic criteria	↓ TSH, ↑ free T4 TSHR-antibody	↑ TSH, ↓ free T4
Complication if untreated	Thyroid storm, IUGR	Anovulation, spontaneous abortion
Outcome if properly treated	Normal pregnancy	Normal pregnancy
Treatment medications	1st trimester: PTU 2nd + 3rd trimester: methimazole	Synthroid (↑ dose 30% above prepregnancy)

SEIZURE DISORDERS

A 25-year-old primigravida is 19 weeks' gestation. She has a 10-year history of generalized seizures poorly controlled requiring hydantoin and valproic acid. A triple marker screen result showed an elevated maternal serum alpha feto protein.

The prevalence of seizure disorders in women of childbearing age is 0.5%. There are classified as follows:

- **Partial seizures** do not involve both hemispheres. They can be **simple** (no loss of consciousness) or **complex** (consciousness may be impaired).
- **Generalized seizures** involve both hemispheres. They can be **absence** type (duration <20 s [formerly called "petit mal"]) or **tonic-clonic** (duration up to several minutes [formerly called "grand mal"]).

The **effect of pregnancy on seizure disorder** is as follows:

- **Seizures unchanged.** Up to 25% of these women will experience deterioration of seizure control during pregnancy, with 75% seeing no change. The more severe the disorder, the more likely it will worsen.
- **Anticonvulsant metabolism increased.** Seizure medication clearance may be enhanced by higher hepatic microsomal activity, resulting in lower blood levels.

The **effect of seizure disorder on pregnancy** is that pregnancy complications are minimal with appropriate prenatal care and compliance with anticonvulsant medications.

The **effect of anticonvulsants on the fetus and infant** is that congenital malformation rate increase from 3% to >10%. In addition, cerebral palsy, seizure disorders, and intellectual disability are increased in offspring of epileptic women. Maternal phenytoin use is associated with neonatal deficiency of vitamin K-dependent clotting factors: II, VII, IX, and X.

Management. Ensure extra **folic acid supplementation** before conception and during embryogenesis to minimize neural tube defects.

- **Anomaly screening.** Offer triple-marker screen and second trimester sonography to identify neural tube defects (NTDs) or other anomalies.
- **Drug monotherapy.** Use a single drug if possible, at the lowest possible dose, to ensure freedom from seizures.
- **Medication levels.** Monitor anticonvulsant levels each trimester and adjust dose as needed. Prevent seizures to minimize maternal and fetal hypoxia.

DIABETES

A 32-year-old Hispanic multigravida is at 29 weeks' gestation. Her 1-h 50-g glucose screen came back at 175 mg/dL. She is 60 inches tall and weighs 200 pounds. Her pregnancy weight gain has been 30 pounds thus far. Her previous babies weighed 3,800 and 4,200 g.

If a pregnant woman is unable to maintain fasting (FBS) or postchallenge glucose values in the normal pregnant range before or after a standard 100-g glucose challenge, she is considered to have diabetes.

The most common risk factors for gestational diabetes are **obesity, age >30**, and **positive family history**. Other risk factors are fetal macrosomia, unexplained stillbirth or neonatal death, polyhydramnios, and previous traumatic delivery.

Prevalence of glucose intolerance in pregnancy is 2–3%.

Classification is done as follows.

- Gestational diabetes mellitus (**GDM**) (**most common type** with onset during pregnancy) is usually diagnosed in the last half. Pathophysiology involves the diabetogenic effect of human placental lactogen (**hPL**), placental insulinase, cortisol, and progesterone. Within 5–10 years after delivery, 35% of women with GDM will develop overt diabetes.
- **Type 1 DM** is juvenile onset, ketosis prone, insulin-dependent diabetes caused by pancreatic islet cell deficiency.
- **Type 2 DM** is adult onset, ketosis resistant, non–insulin-dependent diabetes caused by insulin resistance.

Table I-10-3. Classification of Diabetes Mellitus by Pathophysiology

Gestational	Pregnancy onset	Insulin resistance
Type 1	Juvenile onset	Ketosis prone
Type 2	Adult onset	Insulin resistance

Table I-10-4. White Classification of Diabetes in Pregnancy

Class A1	GDM with normal FBS not requiring insulin
Class A2	GDM with elevated FBS requiring insulin
Class B	Overt DM onset after age 20 years and duration <10 years
Class C	Overt DM onset age 10–19 years or duration 10–19 years
Class D	Overt DM onset before age 10 years or duration ≥20 years
Class E	Overt DM with calcified pelvic vessels
Class F	Overt DM with nephropathy
Class R	Overt DM with proliferative retinopathy

Screening is performed on **all pregnant women** 24–28 weeks' gestation when the anti-insulin effect of hPL is maximal. On patients with risk factors it is performed on the first prenatal visit, then repeated at 24–28 weeks if initially negative.

- The screening test is a 1-h 50-g oral glucose challenge test (OGTT) with normal values being <140 mg/dL. (A fasting state is not needed.)
- If screening value ≥140 mg/dL, then proceed to a definitive 3-h 100-g OGTT. If screening value ≥200 mg/dL, and an FBS is ≥95 mg/dl, GDM is diagnosed and no further OGTT testing is needed.

Diagnosis. The 3-h OGTT is performed on **all patients who have an abnormal screening test**. Definitive diagnosis is based on an abnormal 3-h 100-g OGTT performed after an overnight fast. Four glucose values are obtained.

- Normal pregnant values are FBS <95 mg/dL, 1 h <180 mg/dL, 2 h <155 mg/dL, 3 h <140 mg/dL. If only one value is abnormal, **impaired glucose tolerance** is diagnosed. If ≥2 values are abnormal, **GDM** is diagnosed.
- If FBS ≥125, overt diabetes is diagnosed and the 100-g glucose load should not be given.

General Management Antepartum

High-Yield

Antepartum glucose management

The most significant factor in management of diabetic pregnancies is achieving maternal euglycemia.

- **American Diabetes Association diet:** 80% of patients with GDM can maintain glucose control with diet therapy. Educate patient regarding spreading calories evenly throughout the day; encourage complex carbohydrates.
- **Home blood glucose monitoring:** Patient checks her own blood glucose values at least 4x/day with target values FBS <90 mg/dL and 1 h after meal <140 mg/dL.
- **Insulin therapy:** Start subcutaneous insulin with type 1 and type 2 DM and with GDM if home glucose values are consistently above the target range. Initial dose is based on pregnancy trimester.

  Total daily insulin units are determined as follows: **actual body weight in kilograms** × **0.8** (first trimester), **1.0** (second trimester), or **1.2** (third trimester).

  Dosing is divided: insulin is divided with 2/3 of total daily dose in morning (split into 2/3 NPH and 1/3 regular) and 1/3 of total daily dose in evening (split into 1/2 NPH and 1/2 regular). Insulin is a large molecule and **does not cross the placenta**. Insulin requirements will normally increase through the course of the pregnancy. About 15% of patients with GDM will require insulin.
- **Oral hypoglycemic agents:** Metformin and glyburide are oral agent options for patients who fail diet therapy and initially decline insulin therapy. Since these oral agents cross the placenta, they are second choice after insulin, which does not. Metformin is preferred because glyburide has a higher failure rate in achieving normoglycemia.

Table I-10-5. Gestational Diabetes

Questions	Criteria/Problems	Diag/Mgmt
1-hr 50g OGTT Screening test	<140 mg/dL	GDM ruled out
3-hr 100g OGTT Definitive diagnosis	≥2 values ↑	GDM diagnosed
Home glucose monitoring	Mean glucose values FBS >90; 1 hr pp >140	Start insulin or glyburide
Fetal demise risk factors	1: needs insulin or glyburide 2: HTN 3: previous demise	Starting 32 wk NST & AFI 2/wk
L&D problems	Arrest stage 1 or 2 Shoulder dystocia	CS if estimated fetal weight >4,500 g
Postpartum management	Prevent postpartum hemorrhage	FBS ≥126 mg/dL 2 hr 75 g OGTT

Antepartum overt diabetes management

- **Hemoglobin A1c.** Obtain a level on the first visit to ascertain degree of glycemic control during the previous 60–120 days. Repeat levels each trimester.
- **Renal status.** Obtain an early pregnancy baseline 24-h urine collection for total protein and creatinine clearance.
- **Retinal status.** Obtain an early pregnancy ophthalmologic funduscopic evaluation for proliferative retinopathy.
- **Home blood glucose monitoring.** Patient checks her own blood glucose values at least four times a day with target values of FBS 60–90 mg/dL and 1 h after a meal of <140 mg/dL.

Preconception anomaly management

- **Anomaly risk.** Women with overt diabetes are at increased risk of fetal anomalies. This risk can be minimized by lifestyle modification. Diabetic embryopathy can affect almost any fetal organ system but the most common findings are CNS (anencephaly, spina bifida), skeletal (caudal regression syndrome, sacral agenesis), and cardiovascular (transposition of the great vessels, ventricular septal defects, atrial septal defects, coarctation of the aorta).
- **Euglycemia.** Maintaining glucose values at normal levels reduces anomaly risk close to that of nondiabetes; start three months prior to discontinuing contraception.
- **Folate supplementation.** Folic acid, 4 mg a day, should be started three months prior to conception to prevent both fetal neural tube defects, as well as congenital heart defects.

Antepartum fetal testing management

- **Anomaly screening.** Anomalies are mediated through hyperglycemia and are highest with poor glycemic control during embryogenesis. **Anomalies are not increased in GDM** because hyperglycemia is not present in the first half of pregnancy. Most common fetal anomalies with overt DM are **NTD and congenital heart disease**. An uncommon anomaly, but one highly specific for overt DM, is **caudal regression syndrome**. Obtain a **quadruple-marker screen** at 16–18 weeks to assess for NTD as well as a targeted ultrasound at 18–20 weeks to look for structural anomalies. If the glycosylated hemoglobin is elevated, order a fetal echocardiogram at 22–24 weeks to assess for congenital heart disease.
- **Fetal growth.** Monthly sonograms will assess fetal macrosomia (most commonly seen) or IUGR (seen with longstanding DM and vascular disease).
- **Fetal surveillance.** Start weekly NSTs and amniotic fluid index (AFIs) at **32 weeks** if taking insulin, macrosomia, previous stillbirth, or hypertension. Start NSTs and AFIs at **26 weeks** if small vessel disease is present or there is poor glycemic control. Biophysical profiles can be performed at the time of monthly sonograms.

General Management Intrapartum

High-Yield

- **Timing of delivery.** Fetal maturity is often delayed in fetuses of diabetic mothers, yet prolonging the pregnancy may increase the risk of stillbirth; delivery planning is a result of balancing these factors. The target delivery gestational age is 39 weeks, but may be necessary earlier in the presence of fetal jeopardy and poor maternal glycemic control. An amniotic fluid lecithin to sphingomyelin **(L/S) ratio of 2.5** in the presence of **phosphatidyl glycerol** ensures fetal lung maturity.

- **Mode of delivery.** The cesarean section rate in diabetic pregnancies approaches 50% because of fetal macrosomia, arrest of labor, and concern regarding shoulder dystocia.
- **Glycemic control.** Maintain maternal blood glucose levels between 80–100 mg/dL using 5% dextrose in water and an insulin drip.

General Management Postpartum

High-Yield

- **Postpartum hemorrhage.** Watch for uterine atony related to an overdistended uterus.
- **Hypoglycemia.** Turn off any insulin infusion because insulin resistance decreases with rapidly falling levels of hPL after delivery of the placenta. Maintain blood glucose levels with a sliding scale.
- **Persistent glucose intolerance.** At 6 weeks postpartum, perform a 2-hour 75-gram OGTT to determine whether the patient has persistent hyperglycemia, which suggests in retrospect that her diagnosis is actually overt type 2 diabetes that just happened to start during pregnancy.

Neonatal Issues Management

High-Yield

- **Hypoglycemia** caused by persistent hyperinsulinemia from excessive prenatal transplacental glucose.
- **Hypocalcemia** caused by failure to increase parathyroid hormone synthesis after birth.
- **Polycythemia** caused by elevated erythropoietin from relative intrauterine hypoxia.
- **Hyperbilirubinemia** caused by liver immaturity and breakdown of excessive neonatal red blood cells (RBCs).
- **Respiratory distress syndrome** caused by delayed pulmonary surfactant production.

ANEMIA

An 18-year-old woman G3 P2 had prenatal laboratory tests drawn when she was seen for her first prenatal visit at 18 weeks' gestation. The complete blood count showed the following: hemoglobin 9.5 g/dL, hematocrit 28%, MCV 75, and RDW 17.0. Her first child was delivered two years ago, with her second child born one year ago.

Anemia is a hemoglobin concentration <10 g/dL during pregnancy or the puerperium. This is less than the 12 g/dL that is the lower limit of normal in the nonpregnant woman.

Iron Deficiency Anemia

High-Yield

Iron deficiency anemia is a nutritional anemia resulting in decreased hemoglobin production. A pregnant woman needs 800 mg of elemental iron; 500 mg goes to expand the RBC mass and 300 mg goes to the fetal-placental unit.

Falling hemoglobin values do not occur until complete depletion of iron stores in the liver, spleen, and bone marrow, which is followed by a decrease in serum iron with increase in total iron binding capacity (TIBC).

Findings may vary from none to general malaise, palpitations, and ankle edema.

Note

Iron deficiency anemia is the **most common** anemia in women because of **menstrual and pregnancy** needs.

OB Triad

Iron Deficiency Anemia

- Hemoglobin <10 g
- MCV <80 μm^3
- RDW >15%

Diagnosis. RBCs are microcytic and hypochromic. Hemoglobin <10 g/dL, MCV <80, RDW >15. A very low serum ferritin (i.e., <15 ng/mL) is diagnostic of iron deficiency.

Risk factors include chronic bleeding, poor nutrition, and frequent pregnancies. Fetal effects include increased IUGR and preterm birth.

Prevention includes elemental iron 30 mg per day.

Treatment. $FeSO_4$ 325 mg po tid.

OB Triad

Folate Deficiency Anemia

- Hemoglobin <10 g
- MCV >100 μm^3
- RDW >15%

Folate Deficiency Anemia

High-Yield

Folate deficiency anemia is a nutritional anemia resulting in decreased hemoglobin production.

Folate stores in the body are usually enough for 90 days. Falling hemoglobin values occur only after folate stores have been completely depleted.

Findings may vary from none to general malaise, palpitations, and ankle edema.

Diagnosis. RBCs are macrocytic. Hemoglobin ≤10 g/dL, MCV >100, RDW >15. RBC folate levels are low. Peripheral smear may show hypersegmented neutrophils.

Risk factors include chronic hemolytic anemias (e.g., sickle cell disease), anticonvulsant use (phenytoin, phenobarbital), and frequent pregnancies. Fetal effects include increased IUGR, preterm birth, and NTD.

Prevention includes folate 0.4 mg po daily for all women and 4 mg po daily for those at high risk for NTDs.

Treatment. Folate 1 mg po daily.

Sickle Cell Anemia

High-Yield

Sickle cell anemia is an inherited autosomal recessive disease resulting in normal production of abnormal globin chains. **Screening tests** are peripheral blood tests used to detect the presence or absence of hemoglobin S; they do not differentiate between disease and trait. A hemoglobin electrophoresis (**diagnostic test**) will differentiate between SA trait (<40% hemoglobin S) or SS disease (>40% hemoglobin S).

African and Mediterranean descent is the only significant **risk factor** for sickle cell anemia.

Effects on pregnancy **with SA** may include increased urinary tract infection but unchanged pregnancy outcome; **with SS**, possible increased spontaneous abortions, IUGR, fetal deaths, preeclampsia, and preterm delivery.

Treatment. Avoid hypoxia, take folate supplements, and monitor fetal growth and well-being. In sickle cell crisis, the patient should be hospitalized and treated with hydration, narcotics for pain, oxygen, and DVT prophylaxis. Avoid hydroxyurea due to teratogenic and neoplastic concerns. Also avoid routine RBC transfusion.

LIVER DISEASE

Intrahepatic Cholestasis of Pregnancy

High-Yield

A 31-year-old primigravida woman with a history of infertility underwent ovulation induction. She is now at 20 weeks' gestation with dizygotic twins of different genders. She is of Swedish descent and complains of intense skin-itching. She has not experienced these symptoms previously. Her sister experienced similar complaints when she was pregnant, and delivered her baby prematurely. No identifiable rash is noted on physical examination. She states that her urine appears dark-colored.

Intrahepatic cholestasis is stimulated by estrogen in genetically predisposed women in the second half of pregnancy. Bile acids are incompletely cleared by the liver and accumulate in the plasma. There is a high recurrence rate with subsequent pregnancies. It is the most common liver disease unique to pregnancy.

The overall prevalence is 0.5% in North America and Europe. Risk is increased in Chile, Finland, and Sweden, (as is twin pregnancy).

Clinical Findings. The most significant symptom is intractable pruritus on the palms and soles of the feet—worse at night—without specific skin findings. Lab tests show a mild elevation of bilirubin but diagnostic findings are serum bile acids increased 10- to 100-fold.

There is no adverse effect on maternal outcome, but preterm births and stillbirths are increased.

Management. Oral antihistamines for mild cases. Cholestyramine has been used to decrease enterohepatic circulation.

- **Ursodeoxycholic acid is the treatment of choice.** Antenatal fetal testing should be initiated at 34 weeks. Symptoms disappear after delivery.
- Induce labor at 37 weeks gestation.

Acute Fatty Liver

High-Yield

A 29 year-old primigravida is at 33 weeks' gestation. She is brought to the maternity unit by her husband who states she is becoming mentally confused. He reports she started experiencing nausea and vomiting three days ago which are becoming worse, associated with lack of appetite. Fundal height is 30 cm. Fetal heart rate 145/min with non-reactive non-stress test, BP 150/95 mm Hg, random blood glucose 52 mg/dL. Platelet count is 75,000 and PTT is prolonged at 64.7 seconds. Creatinine is 2.1 mg/dL. Uric acid is 11.9 mg/dL, lactic dehydrogenase 1063 U/l, ALT 220 U/l, AST 350 U/l, total bilirubin 8.4 mg/dL. Serum ammonia is elevated. Urine protein dipstick is 3+.

Acute fatty liver is a rare, life-threatening complication of pregnancy that usually occurs in the third trimester. Prevalence is 1 in 15,000. Maternal mortality rate is 20%. It is thought to be caused by a disordered metabolism of fatty acids by mitochondria in the fetus, caused by deficiency in the long-chain 3-hydroxyacyl-coenzyme A dehydrogenase (LCHAD) enzyme.

Clinical Findings. Symptom onset is gradual, with nonspecific flulike symptoms including nausea, vomiting, anorexia, and epigastric pain.

- Jaundice and fever may occur in as many as 70% of patients.
- Hypertension, proteinuria, and edema can mimic preeclampsia.
- This may progress to involvement of additional systems, including acute renal failure, pancreatitis, hepatic encephalopathy, and coma. Laboratory findings may include: moderate elevation of liver enzymes (e.g., ALT, AST, GGT), hyperbilirubinemia, DIC.
- **Hypoglycemia** and **increased serum ammonia** are unique laboratory abnormalities.

Management. Intensive care unit stabilization with acute IV hydration and monitoring is essential. Prompt delivery is indicated. Resolution follows delivery if the mother survives.

URINARY TRACT INFECTIONS

> A 23-year-old primigravida at 31 weeks' gestation comes to the birthing unit with complaints of flank pain, nausea, vomiting, and shaking chills for the past 12 h. She has been diagnosed with sickle cell trait. On examination her temperature is 39.4 C (103 F), pulse 125 beats/min, and respirations 30 breaths/min. Her skin is grossly diaphoretic and she has exquisite right costovertebral angle tenderness. Electronic fetal monitoring shows baseline pulse 170/min with reactivity. Uterine contractions are noted every 10 min.

Urinary tract infections (UTI) may involve the **lower tract** (including the bladder or urethra) or **upper tract** (including the kidney). The most common organisms are **gram-negative enteric bacteria** with *Escherichia coli* the most frequent.

Pregnancy is a risk factor. Others include mechanical urinary obstructions and systemic diseases (such as sickle cell trait/disease, diabetes mellitus, and gout).

Asymptomatic Bacteriuria

High-Yield

OB Triad

Asymptomatic Bacteriuria

- No urgency, frequency, or burning
- No fever
- Urine culture (+)

Asymptomatic bacteriuria is the **most common** UTI in pregnancy. If not treated, 30% of cases will develop acute pyelonephritis.

Clinical Findings. No symptoms or signs are present.

Diagnosis is made with a positive urine culture showing >100K colony-forming units (CFU) of a single organism.

Treatment. Single-agent, outpatient oral antibiotics.

Acute Cystitis

High-Yield

OB Triad

Acute Cystitis

- Urgency, frequency, and burning
- No fever
- Urine culture (+)

Acute cystitis is a UTI localized to the bladder without systemic findings. If not treated, 30% of cases will develop acute pyelonephritis.

Clinical Findings. Urgency, frequency, and burning are common.

Diagnosis is made with a positive urine culture showing >100 K CFU of a single organism.

Treatment. Single-agent, outpatient oral antibiotics.

Acute Pyelonephritis

High-Yield

Acute pyelonephritis is a UTI involving the upper urinary tract with systemic findings. It is one of the **most common** serious medical complications of pregnancy.

Preterm labor and delivery can occur. Severe cases are complicated by sepsis, anemia, and pulmonary dysfunction, sometimes requiring ICU care, including intubation.

Clinical Findings. Symptoms include shaking chills, anorexia, nausea, vomiting, and flank pain. Signs include high fever, tachycardia, and costovertebral angle tenderness (R > L).

Diagnosis is confirmed with a positive urine culture showing >100 K CFU of a single organism.

Treatment. Hospital admission, generous IV hydration, parenteral antibiotics e.g., ceftriaxone, and tocolysis as needed.

OB Triad

Acute Pyelonephritis

- Urgency, frequency, and burning
- Fever and costovertebral angle tenderness (CVAT)
- Urine culture (+)

THROMBOPHILIAS

> A 26-year-old G4 P1 Ab2 woman comes in for her first prenatal visit at 8 weeks' gestation by dates. Her first pregnancy was a spontaneous first-trimester loss, for which she underwent a D&C. In her second pregnancy she developed right lower extremity deep venous thrombosis at 29 weeks, which was followed by an unexplained fetal demise at 30 weeks. Labor was induced with PGE2. The fetus was normal in appearance, without congenital anomalies. Autopsy on the fetus was unremarkable. Her last pregnancy was also a spontaneous first-trimester loss. Her sister has a history of recurrent deep venous thrombosis.

The thrombophilias are disorders which promote blood clotting due to an excess of clotting factors or a deficiency of anticlotting proteins that limit clot formation. Prevalence is as high as 20% of the population, but most individuals are asymptomatic. Some will develop deep vein thrombosis or venous thromboembolism (VTE) that can become life-threatening.

Risk factors include immobilization, surgery, or pregnancy. Pregnant women with a thrombophilia are also at higher risk than other pregnant women of developing a VTE.

Pulmonary embolus is the leading cause of maternal death in the United States; >50% of pregnant women who develop a pulmonary embolus or other VTE have an underlying thrombophilia.

Diagnosis. Indications for testing are history of VTE or first-degree relative with high-risk thrombophilia or VTE age <50 years.

- **Inherited thrombophilias to test for** include factor V Leiden (FVL) mutation, prothrombin gene mutation (PGM) G2021 OA, protein C deficiency (PCD), protein S deficiency (PSD), and antithrombin deficiency (ATD).
  - **High risk** thrombophilias include homozygous FVL or PGM; compound heterozygote FVL and PTM; and all ATD.
  - **Low risk** thrombophilias include heterozygous FVL or PGM; and all PCD & PSD.

- **Acquired thrombophilias to test for** include antiphospholipid syndrome (APS). One or more of the following three antiphospholipid antibodies must be positive on ≥2 occasions at least 12 weeks apart.
  - Lupus anticoagulant
  - Anticardiolipin antibody (lgG & IgM)
  - Anti-β_2-glycoprotein 1 (lgG & IgM)

Treatment. Anticoagulation options:

- **Unfractionated heparin** (UFH) can be used antepartum & postpartum.
  - Advantages: inexpensive, can be reversed with protamine sulfate
  - Disadvantages: cannot use orally, short half-life, needs monitoring with aPTT levels, heparin-induced osteopenia, heparin-induced thrombocytopenia (HIT)
- **Low molecular weight heparin** (LMWH) can be used antepartum & postpartum.
  - Advantages: longer half-life, less need for monitoring with antifactor Xa levels
  - Disadvantages: cannot use orally, higher cost, can not be reversed
- **Warfarin (Coumadin)** can be used only postpartum.
  - Advantages: oral administration, long half-life, inexpensive, OK for breast feeding
  - Disadvantages: crosses placenta, needs monitoring with INR

For anticoagulation medications, use the following guidelines:

Antepartum: Use LMWH from first trimester to 36 weeks; then at 36 weeks transition to UFH until delivery.

- **None or prophylactic dose**
  - Low-risk thrombophilia without VTE episode
- **Prophylactic or intermediate-dose**
  - Low-risk thrombophilia with single VTE episode
  - High-risk thrombophilia without VTE episode
- **Therapeutic dose**
  - High-risk thrombophilia with single VTE episode
  - Any thrombophilia with VTE in current pregnancy

Intrapartum

- Discontinue UFH during immediate peripartum interval to decrease risk of hemorrhage and permit regional anesthesia.
- Protamine sulfate can be used to reverse UFH effect.

Postpartum

- VTE risk increased 20-fold in the first week postpartum.
- All patients at risk should be receive postpartum anticoagulation even if they did not receive it antepartum.
- Resume anticoagulation 6 hours after vaginal delivery and 12 hours after cesarean section.
- Warfarin (Coumadin) is safe for breast feeding moms.

ANTIPHOSPHOLIPID SYNDROME

Antiphospholipid syndrome (APS) is an autoimmune disorder defined by both the presence of characteristic clinical features and circulating antiphospholipid antibodies. Diagnosis requires that at least one clinical and one laboratory criterion are met.

The **clinical criteria** for diagnosis and indications for lab testing include:

- **Vascular thrombosis:** ≥1 clinical thrombotic episodes (arterial, venous, or small vessel)
- **Pregnancy morbidity (unexplained):** ≥1 fetal demise at ≥10 weeks; ≥3 consecutive miscarriages at <10 weeks

The **lab criteria** require that ≥1 of the following antiphospholipid antibodies be positive on ≥2 occasions at least 12 weeks apart.

- Lupus anticoagulant
- Anticardiolipin antibody (lgG & IgM)
- Anti-beta-2-glycoprotein I (lgG & IgM)

Management. For antepartum anticoagulation management, the following is recommended:

- APS without a thrombotic event: no heparin or only prophylactic heparin
- APS with a thrombotic event: prophylactic heparin

For all women with APS, the following general management is recommended:

- Antepartum: sono assessment of fetal growth monthly; modified Biophysical Profile weekly starting at 32 weeks
- Intrapartum: stop anticoagulation
- Postpartum: resume or start anticoagulation in 6 hours (after vaginal delivery) or 12 hours (after cesarean section); continue anticoagulation for 6 weeks using either heparin or warfarin (safe for breast feeding moms); avoid estrogen-containing contraceptives

Thromboembolism

The mediating factor is frequently endothelial injury from traumatic delivery or cesarean section. In the postpartum period, the risk is increased fivefold. Vascular stasis is the strongest predisposing factor, with decreased pelvic and lower extremity blood flow. Enhanced blood coagulability in pregnancy is due to increased factors II, VII, VIII, IX, and X. Risk is even more elevated if the patient has coagulation protein deficiencies: antithrombin III, protein C, protein S, and plasminogen.

Superficial Thrombophlebitis

Superficial thrombophlebitis does not predispose to thromboembolism but may mimic more severe disease.

- **Clinical Findings:** Symptoms include localized pain and sensitivity. Signs include erythema, tenderness, and swelling. Diagnosis is one of exclusion after ruling out DVT.
- **Management:** Treatment is conservative: bed rest, local heat, NSAIDs.

Deep Venous Thrombosis (DVT)

DVT **does** predispose to thromboembolic disease. The site of thrombosis is typically in the lower half of the body. Half of cases occur in the pelvic veins and half occur in the lower extremities.

- **Clinical Findings:** Symptoms may include pain and increased skin sensitivity, but there may be no complaints. Signs may include calf pain on foot dorsiflexion (Homan sign), although these findings are not highly sensitive or specific. Diagnosis is by duplex Doppler.
- **Management:** Full anticoagulation with IV heparin to increase PTT by 1.5–2.5 times the control value. Once therapeutic levels are achieved, subcutaneous heparin is used once. No warfarin is used antepartum because of teratogenicity concerns with the fetus. Perform thrombophilia workup.

Pulmonary Embolus

Pulmonary embolus (PE) is a potentially fatal result of DVT in which emboli travel through the venous system to the lungs. The source of the emboli is most commonly in the lower extremities or pelvis.

- **Clinical Findings:** Symptoms include chest pain and dyspnea (80%) but no single symptom(s) predominate because thrombi location varies. Physical and imaging findings include:
  - Tachypnea (90%)
  - **Chest x-ray** often normal
  - **ABG** showing low pO_2 (but often in the normal range)
  - **EKG** that may show tachycardia
  - Right axis deviation (but usually is normal)
- **Diagnosis** depends on the pulmonary imaging modalities used. Spiral CT scan of the chest is the best initial test for suspected PE. **Pulmonary angiography** is the most definitive diagnostic method; most common indication is a negative spiral CT scan in a high-risk and symptomatic patient.
- **Management:** Full anticoagulation (IV, SQ) heparin to increase PTT by 1.5–2.5 times the control value. No warfarin is used antepartum due to teratogenic concerns. Perform thrombophilia workup.

Disproportionate Fetal Growth 11

Learning Objectives

- ❏ Demonstrate understanding of intrauterine growth restriction
- ❏ Answer questions about macrosomia

INTRAUTERINE GROWTH RESTRICTION

The **common definition** of intrauterine growth restriction (IUGR) (also known as fetal growth restriction) is a fetus with estimated fetal weight (EFW) $<5-10^{th}$ percentile for gestational age. This assumes the fetus is not growing to its genetic potential.

Another definition is <2,500 grams (5 lb, 8 oz). Clearly, neonatal morbidity and mortality are affected by lowering birth weight. However, **70% of these fetuses are constitutionally small**.

Dating. Accurate early pregnancy dating is essential for making the diagnosis. An early sonogram (<20 weeks) is most accurate if conception date is unknown. **Don't change gestational age based on a late sonogram**.

Fetal Causes. Examples include aneuploidy (e.g., T21, T18, T13); infection (e.g., TORCH), structural anomalies (e.g., congenital heart disease, neural tube defects, ventral wall defects). These causes typically lead to **symmetric** IUGR.

Placental Causes. Examples include infarction, abruption, twin-twin transfusion syndrome (TTTS), velamentous cord insertion. These causes typically lead to **asymmetric** IUGR.

Maternal Causes. Examples include hypertension (e.g., chronic, preeclampsia), small vessel disease (e.g., SLE, long-standing type 1 diabetes), malnutrition, tobacco, alcohol, street drugs. These causes typically lead to **asymmetric** IUGR.

Symmetric IUGR

High-Yield

- All ultrasound parameters (HC, BPD, AC, FL) are smaller than expected.
- Etiology is **decreased growth potential**, i.e., aneuploidy, early intrauterine infection, gross anatomic anomaly.
- Workup should include detailed sonogram, karyotype, and screen for fetal infections.
- **Antepartum tests are usually normal**.

OB Triad

Symmetric IUGR

- Head and abdomen both small
- Etiology: fetal (aneuploidy, infection, anomaly)
- Decreased growth potential

OB Triad

Asymmetric IUGR

- Head normal; abdomen small
- Etiology: maternal-fetal (inadequate nutritional substrates)
- Decreased placental perfusion

Asymmetric IUGR

High-Yield

- Ultrasound parameters show **head sparing**, but **abdomen is small**.
- Etiology is **decreased placental perfusion** due to chronic maternal diseases (hypertension, diabetes, SLE, cardiovascular disease) or abnormal placentation (abruption and infarction).
- Amniotic fluid index is often decreased, especially if uteroplacental insufficiency is severe.
- **Monitoring** is with serial sonograms, non-stress test, amniotic fluid index, biophysical profile, and umbilical artery Dopplers.

MACROSOMIA

Macrosomia is a fetus with estimated fetal weight (EFW) >90–95th percentile for gestational age. Birth weight ≥4,000–4,500 grams (8 lb, 13 oz to 9 lb, 15 oz).

Sonogram EFW. Accuracy in estimating birth weight is poor. Errors in prediction of EFW at term are ±400 grams.

Risk Factors. Gestational diabetes mellitus, overt diabetes, prolonged gestation, increase in BMI (obesity), increase in pregnancy weight gain, multiparity, male fetus.

Maternal Hazards. Operative vaginal delivery, perineal lacerations, postpartum hemorrhage (uterine atony), emergency cesarean section, pelvic floor injury.

Fetal Hazards. Shoulder dystocia, birth injury, asphyxia.

Neonatal Hazards. Neonatal intensive care admission, hypoglycemia, Erb's palsy.

Prevention. No accurate ways of predicting or prevention are currently available.

Management. Consider elective cesarean (if EFW >4,500 g in diabetic mother or >5,000 g in nondiabetic mother) or early induction, but this may result in increased cesarean delivery rate due to failure of induction.

Antepartum Fetal Testing 12

Learning Objective

- ❑ Describe the appropriate use of antepartum fetal testing including nonstress test, amniotic fluid index, biophysical profile, contraction stress test, and umbilical artery Doppler

OVERVIEW

A 37-year-old multipara with systemic lupus erythematosus is at 31 weeks' gestation. She has chronic hypertension that is being controlled with methyldopa. She comes to the office stating her fetus is not moving as much as it used to.

Antenatal fetal tests are highly accurate in confirming fetal well-being but are poor predictors of fetal jeopardy. The most common reasons for fetal testing are decreased fetal movements, diabetes, post dates, chronic hypertension, and IUGR.

NONSTRESS TEST

The nonstress test (NST) assesses the frequency of fetal movements using an external fetal heart rate (FHR) monitoring device to detect the presence or absence of accelerations. These are abrupt increases in FHR above the baseline lasting <2 min and are unrelated to contractions. The criteria vary by gestational age:

- <32 weeks, the increase should be ≥10 beats/min lasting ≥10 s
- >32 weeks, the increase should be ≥15 beats/min lasting ≥15 s

They are mediated by the **sympathetic** nervous system and always occur in response to **fetal movements**. **Interpretation: accelerations are always reassuring**.

- **Reactive NST** requires the presence of 2 accelerations in a 20 min window of time meeting the above criteria. This is reassuring and highly predictive for fetal well-being. Fetal death rate is only 3 per 1,000 in the next week. **Management** is weekly NST.
- **Nonreactive NST** is diagnosed when any criteria for reactivity are not met: either the number of accelerations in 20 min or the amplitude or duration of the acceleration. 80% of nonreactive NSTs are false positives (meaning the fetus is not hypoxemic). Nonhypoxemic causes include fetal sleep, prematurity, drug effects, and CNS anomalies. **Management** is fetal vibroacoustic stimulation to see whether this results in reactivity. If the NST is persistently nonreactive, perform a biophysical profile.

Table I-12-1. Nonstress Test (NST)

Reactive NST	**Criteria:** ≥2 accelerations in 20 min: ↑ FHR ≥15 beats/min and lasting ≥15 seconds
	Assessment: reassuring of fetal well-being
	Follow-up: repeat weekly/biweekly
Nonreactive NST	**Criteria:** no fetal heart rate accelerations or did not meet criteria
	Assessment: sleeping, immature, or sedated fetus; acidotic, compromised fetus?
	Follow-up: vibroacoustic stimulation
	If still NR: do contraction stress test or biophysical profile

AMNIOTIC FLUID ASSESSMENT

In the third trimester, the volume of amniotic fluid is considered to largely reflect a balance between fetal urine production and fetal swallowing. If fluid is low (**oligohydramnios**) consideration must be given to problems with urinary tract anomalies or renal perfusion. If fluid is excessive (**polyhydramnios**) consideration must be given to problems with the decreased fetal swallowing or GI tract anomalies.

Third trimester assessment of amniotic fluid uses ultrasound measurement:

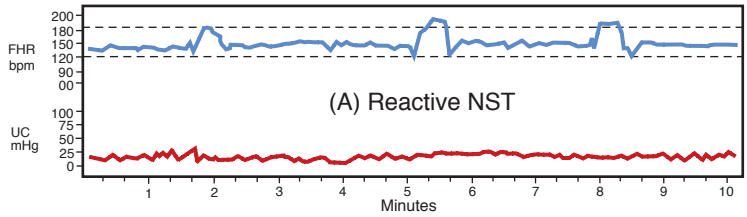
- **Single deepest pocket (SDP)** or maximum vertical pocket (MVP): This is the vertical dimension (in cm) of the largest pocket of AF not persistently containing umbilical cord or fetal extremities. The horizontal measurement of the pocket must be at least 1 cm.
  - Oligohydramnios: depth <2 cm
  - Normal: depth >2 cm and <8 cm
  - Polyhydramnios: depth >8 cm
- **Amniotic fluid index (AFI):** The four-quadrant AFI assesses (in cm) the deepest vertical AF pocket in each of the four quadrants of the uterus. The sum of the AF pocket dimensions is known as the AFI.
  - Oligohydramnios: <5 cm
  - Normal: 5–24 cm
  - Polyhydramnios: >25 cm

BIOPHYSICAL PROFILE (BPP)

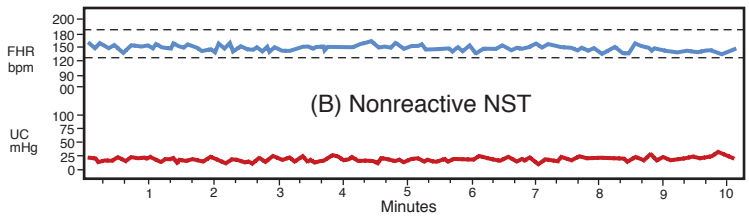
A complete BPP measures **five components of fetal well-being**: NST, amniotic fluid volume, fetal gross body movements, fetal extremity tone, and fetal breathing movements. The last four components are assessed using obstetric ultrasound. Scores given for each component are 0 or 2, with maximum possible score of 10 and minimum score of 0.

- **Score of 8 or 10:** highly **reassuring** of fetal well-being. Management is to repeat the test weekly or as indicated. Fetal death rate is only 1 per 1,000 in the next week.
- **Score of 4 or 6:** worrisome. Management is delivery if the fetus is ≥36 weeks or repeat the biophysical profile in 12–24 h if <36 weeks. An alternative is to perform a CST.
- **Score of 0 or 2:** highly predictive of fetal **hypoxia** with low probability of false positive. Management is prompt delivery regardless of gestational age.

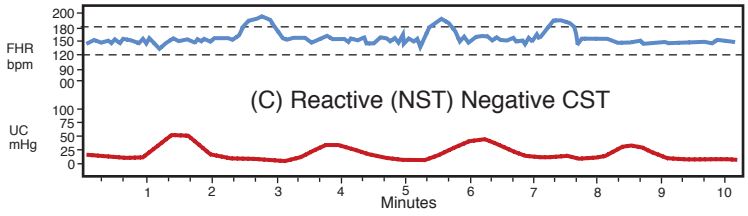
A **modified BPP** includes only the NST and amniotic fluid volume. Its predictive value is almost as high as a complete BPP.



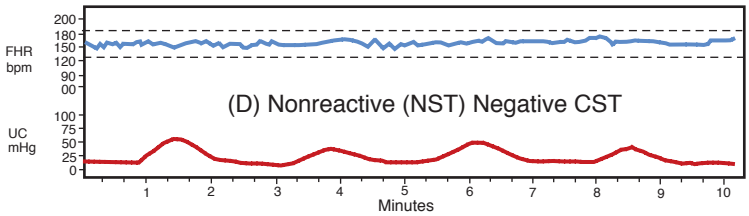
(A) Normal baseline range, and no UCs are present. Thus, only the NST component can be assessed. Because 3 accelerations are present, the assessment is reactive NST. **This is a reassuring tracing.**



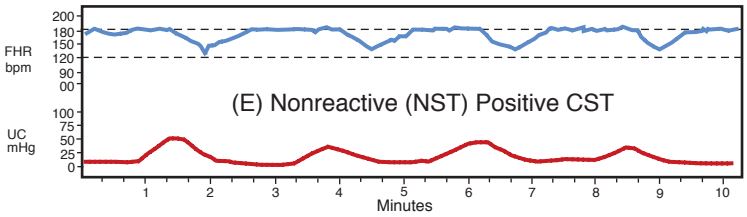
(B) Normal baseline range and no UCs are present. Thus, only the NST component can be assessed. Because no accelerations are present, the assessment is nonreactive NST. Because **this is not a reassuring tracing**, the next step should be a vibroacoustic fetal stimulation.



(C) Normal baseline range and 4 UCs are present in 10 minutes. Thus, both the NST and CST components can be assessed. Because 3 accelerations are present, and no late decelerations are present, the assessment is reactive NST, negative CST. This is a reassuring tracing.



(D) Normal baseline range and 4 UCs are present in 10 minutes. Thus, both the NST and CST components can be assessed. Even though no accelerations can be seen, no late decelerations are present. The assessment is nonreactive NST, negative CST. **This suggests fetal sleep, sedation, or central nervous system (CNS) abnormality.**



(E) Elevated baseline range and 4 UCs are present in 10 minutes. Thus, both the NST and CST components can be assessed. No accelerations can be seen, but repetitive late decelerations are present. The assessment is nonreactive NST, positive CST. **This is highly suggestive of fetal compromise.**

Figure I-12-1. Antepartum Electronic Fetal Monitor (EFM) Tracings

Note

All EFM tracings should be evaluated for the NST and the CST. If a technically adequate FHR tracing is present, the NST component can be assessed as reactive or nonreactive.

If ≥3 UCs are present in 10 minutes, the CST components can be assessed as negative or positive.

CONTRACTION STRESS TEST

The contraction stress test (CST) assesses the ability of the fetus to tolerate transitory decreases in intervillous blood flow that occur with uterine contractions. It uses both external FHR and contraction monitoring devices and is based on the presence or absence of **late decelerations.** These are **gradual** decreases in FHR below the baseline with onset to nadir of ≥30 s. The deceleration onset and end is **delayed** in relation to contractions. If 3 contractions in 10 min are not spontaneously present, they may be induced with IV oxytocin infusion or nipple stimulation. This test is **rarely performed** because of the cost and personnel time required. The most common indication is a **BPP of 4 or 6**.

- **Negative CST** requires absence of any late decelerations with contractions. This is reassuring and highly reassuring for fetal well-being. Management is to repeat the CST weekly. Fetal death rate is only 1 per 1,000 in the next week.
- **Positive CST** is worrisome. This requires the presence of late decelerations associated with at least 50% of contractions. 50% of positive CSTs are false-positive (meaning the fetus is not hypoxemic). They are associated with good FHR variability. The 50% of true-positives are associated with poor or absent variability. Management is prompt delivery.
- Contraindications include situations when contractions would be hazardous to the mother or fetus, e.g., previous classical uterine incision, previous myomectomy, placenta previa, incompetent cervix, preterm membrane rupture, and preterm labor.

Table I-12-2. Contraction Stress Test (CST)

Negative CST	No **late decelerations** are seen in the presence of 3 uterine contractions in 10 min
	Assessment: reassuring of fetal well-being
	Follow-up: repeat CST weekly as needed
Positive CST	Repetitive **late decelerations** are seen in the presence of 3 uterine contractions in 10 min
	Assessment: worrisome, especially if nonreactive non-stress test
	Follow-up: prompt delivery

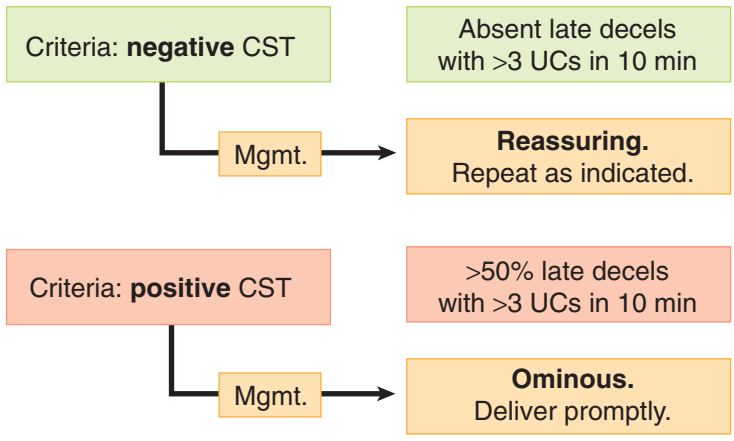


Figure I-12-2. Contraction Stress Test

UMBILICAL ARTERY DOPPLER

This test measures the ratio of systolic and diastolic blood flow in the umbilical artery (UA). The umbilical circulation normally has low resistance, so significant diastolic blood flow is expected. The systolic/diastolic (S/D) ratio normally decreases throughout pregnancy.

The test is predictive of poor perinatal outcome only in IUGR fetuses. Nonreassuring findings, which may indicate need for delivery, are absent diastolic flow and reversed diastolic flow.

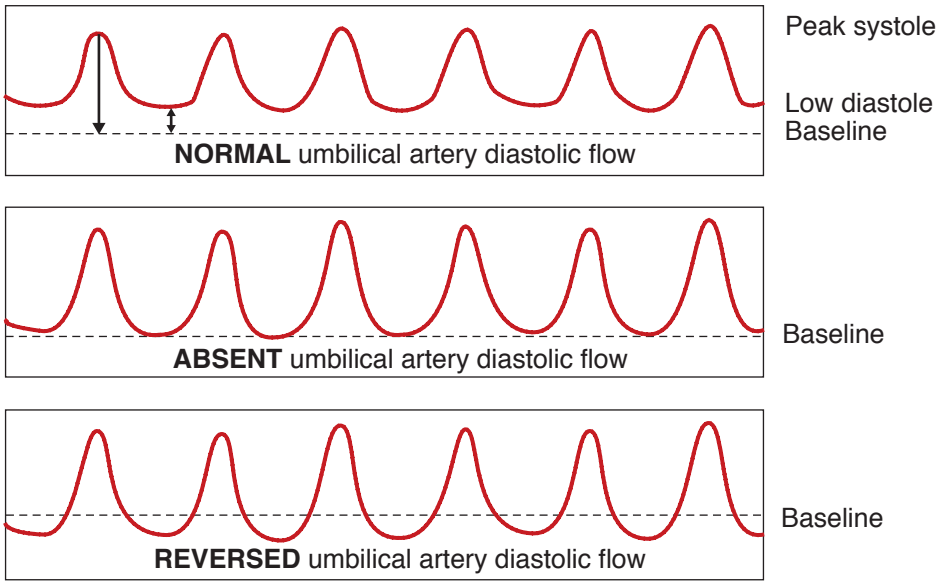


Figure I-12-3. UA Doppler Waveform Patterns

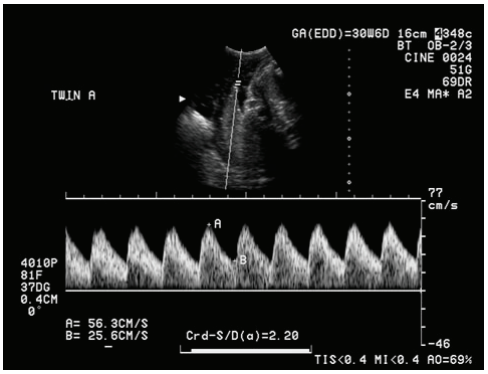


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Figure I-12-4. Normal UA Diastolic Flow

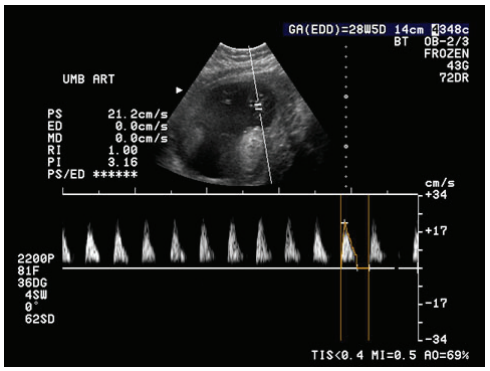

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Figure I-12-5. Absent UA Diastolic Flow

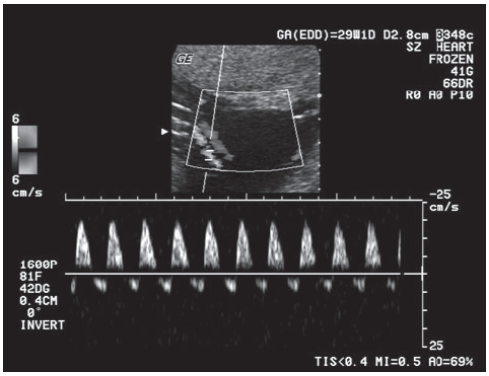

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Figure I-12-6. Reversed Umbilical Artery Diastolic Flow

Fetal Orientation in Utero 13

Learning Objective

- ❑ List the possible fetal orientations in utero and their relation to potential complications of delivery

ORIENTATION IN UTERO

Orientation of the long axis of the fetus to the long axis of the uterus. The **most common lie is longitudinal** (99% of fetuses at term).

- **Longitudinal:** fetus and mother in same vertical axis
- **Transverse:** fetus at right angle to mother
- **Oblique:** fetus at 45° angle to mother

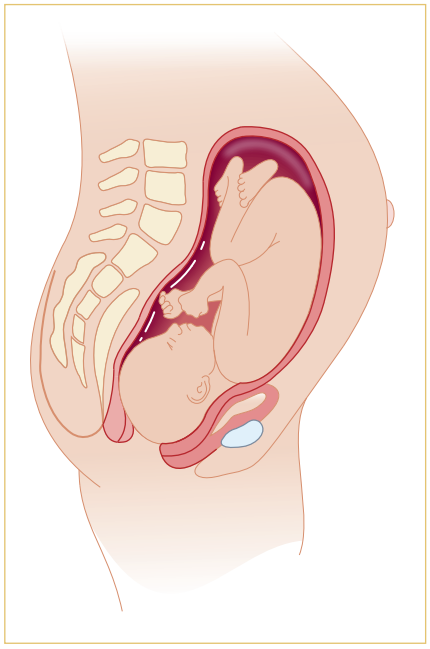


Figure I-13-1. Longitudinal Fetal Lie

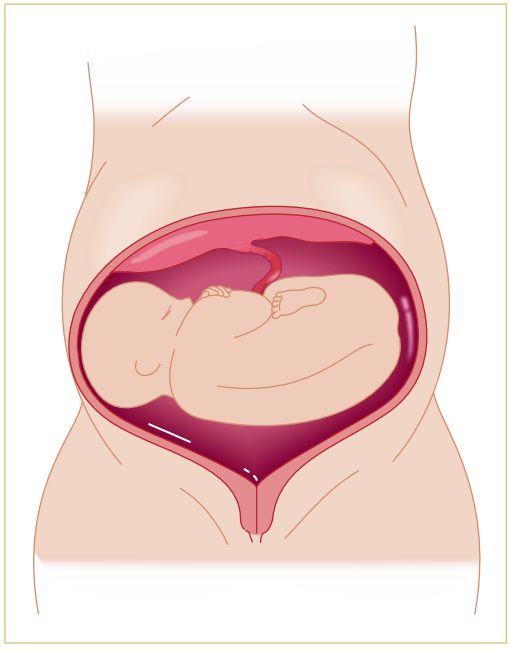


Figure I-13-2. Transverse Fetal Lie

Presentation

High-Yield

Portion of the fetus overlying the pelvic inlet. The **most common presentation is cephalic** (96% of fetuses at term).

- **Cephalic:** head presents first
- **Breech:** feet or buttocks present first. The major risk of vaginal breech delivery is entrapment of the after-coming head.
  - **Frank** breech means thighs are flexed and legs extended. This is the only kind of breech that potentially could be safely delivered vaginally.
  - **Complete** breech means thighs and legs flexed.
  - **Footling** breech means thighs and legs extended.
- **Compound:** more than one anatomic part is presenting (e.g., head and upper extremity)
- **Shoulder:** presents first

OB Triad

Breech Presentations

- Frank: thighs flexed, legs extended
- Complete: thighs and legs flexed
- Footling: thighs and knees extended

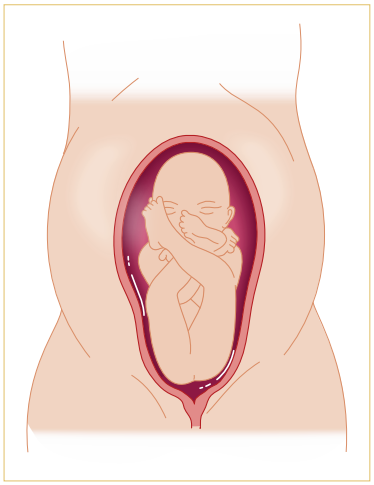


Figure I-13-3. Frank Breech

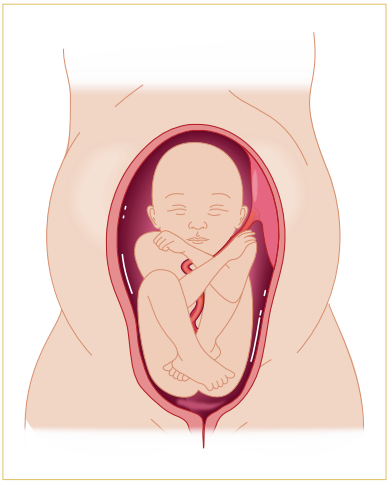


Figure I-13-4. Complete Breech

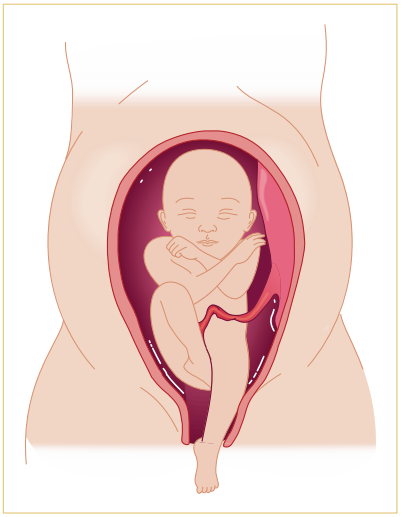


Figure I-13-5. Footling Breech

Position

Relationship of a definite presenting fetal part to the maternal bony pelvis. It is expressed in terms stating whether the orientation part is anterior or posterior, left or right. The **most common position at delivery is occiput anterior**.

- **Occiput:** with a flexed head (cephalic presentation)
- **Sacrum:** with a breech presentation
- **Mentum (chin):** with an extended head (face presentation)

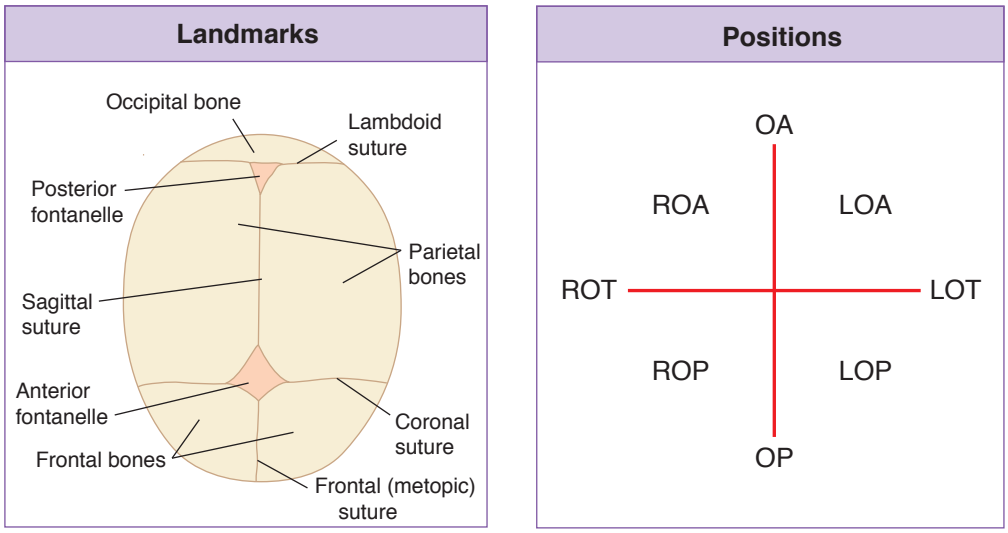


Figure I-13-6. Landmarks and Positions

Attitude

Degree of extension-flexion of the fetal head with cephalic presentation. The **most common attitude is vertex**.

- **Vertex:** head is maximally flexed
- **Military:** head is partially flexed
- **Brow:** head is partially extended
- **Face:** head is maximally extended

Station

High-Yield

Degree of descent of the presenting part through the birth canal; expressed in centimeters above or below the maternal ischial spine.

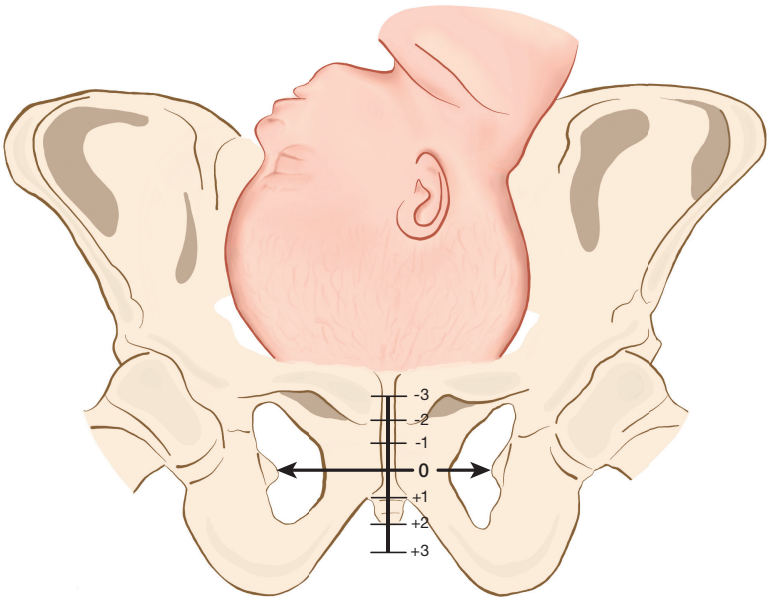


Figure I-13-7. Station of Fetal Head Descent

Normal and Abnormal Labor 14

Learning Objectives

- ❏ List the normal stages of labor and abnormalities that can occur in the process
- ❏ Describe the risks and management of obstetric complications during labor

OVERVIEW OF LABOR

Labor is a process whereby over time regular uterine contractions bring about progressive effacement and dilation of the cervix, resulting in delivery of the fetus and expulsion of the placenta. Contractions will occur at least every 5 min lasting 30 s.

Physiology. Increasing frequency of contractions is associated with the formation of **gap junctions** between uterine myometrial cells. These events are correlated with increasing levels of **oxytocin** and **prostaglandins** along with multiplication of specific **receptors**.

Uterine Changes. The contractile **upper uterine segment**, containing mostly smooth muscle fibers, becomes thicker as labor progresses, exerting forces that expel the fetus down the birth canal. The **lower uterine segment**, containing mostly collagen fibers, passively thins out with contractions of the upper segment.

Cervical Effacement. Cervical softening and thinning occur as increasing levels of oxytocin and prostaglandins lead to breakage of **disulfide linkages** of collagen fibers, resulting in increasing water content. Effacement is often expressed in percentages with the uneffaced (0%) cervix assumed to be 2 cm long and 2 cm wide. Progressive shortening and thinning lead to full effacement (100%) in which the cervix has no length and is paper-thin.

Cervical Dilation. This occurs as the passive lower uterine segment is thinned and pulled up by the contractile upper segment. In early labor (latent phase), the rate of dilation is slow, but at 6 cm of dilation, the rate accelerates to a maximum rate in the active phase of labor. Complete dilation is expressed as 10 cm.

Cardinal Movements of Labor. The first three steps occur **simultaneously**.

- **Engagement:** movement of the presenting part below the plane of the pelvic inlet
- **Descent:** movement of the presenting part down through the curve of the birth canal
- **Flexion:** placement of the fetal chin on the thorax

The next four steps occur **in order**.

- **Internal rotation:** rotation of the position of the fetal head in the mid pelvis from transverse to anterior-posterior
- **Extension:** movement of the fetal chin away from the thorax
- **External rotation:** rotation of the fetal head outside the mother as the head passes through the pelvic outlet
- **Expulsion:** delivery of the fetal shoulders and body

STAGES OF LABOR

Labor refers to the complex process through which **uterine contractions** bring about progressive **dilation**/opening and **effacement**/thinning of the cervix leading to descent of the fetus through the birth canal ending with expulsion of the neonate from the mother's body.

A labor curve shows the change in cervical dilation over time. **Older studies** (Friedman, 1954) were based on 500 women at a single U.S. hospital. That labor curve is not applicable to today's obstetric patients. Today's population has a higher BMI than 60 years ago. This, along and changing obstetric and anesthesia practices, have led to new normal labor curves based on more current data.

Newer studies (Zhang et al, 2010) based on >60,000 laboring women at 19 U.S. medical centers produce contemporary labor curves and norms which differ significantly from the older Friedman data. The new data suggest the following:

- **Transition from latent to active phase is at 6 cm**, rather than 4 cm.
- Rate of active phase cervical **dilation curve is much slower** than previously thought.

Table I-14-1. Stages of Labor

Labor Stage	Definition	Function	Duration
Stage 1—Latent phase Effacement	Begins: onset of regular uterine contractions Ends: acceleration of cervical dilation	**Prepares cervix for dilation**	<20 hours in primipara <14 hours in multipara
Stage 1—Active phase Dilation	Begins: acceleration of cervical dilation Ends: 10 cm (complete)	**Rapid cervical dilation**	≥0.7 cm/hours primipara ≥1.0 cm/hours multipara
Stage 2 Descent	Begins: 10 cm (complete) Ends: delivery of baby	**Descent of the fetus**	<3 hours in primipara <2 hours in multipara Add 1 hour if epidural
Stage 3 Expulsion	Begins: delivery of baby Ends: delivery of placenta	**Delivery of placenta**	<30 minutes

Stage 1 begins with onset of regular uterine contractions and ends with complete cervical dilation at 10 cm. Identification when regular contractions began is often imprecise. Stage 1 of labor is divided into a **latent** and an **active** phase.

- **Latent phase** begins with onset of regular contractions and ends with the acceleration of cervical dilation. Its **purpose** is to soften and efface the cervix preparing it for rapid dilation
  - Minimal descent of the fetus through the birth canal occurs.
  - **Rate of dilation is slower than previous studies showed and is similar in both multiparas and nulliparas.**

  - Both nulliparas and multiparas may take up **6 h** to dilate from 4–5 cm; and up to **3 h** to dilate from 5–6 cm.
  - Although the upper limit of latent phase **duration** may be up to **20 h** in a primipara and up to **14 h** in a multipara, this is never an indication for cesarean section.
- **Active phase** begins with cervical dilation acceleration ending with complete cervical dilation. Cervical dilation of 6 cm should be considered the threshold for active phase.
  - **Cardinal movements of labor occur**, with beginning descent of the fetus in the latter part of this phase.
  - **Slow but progressive labor in first stage of labor is normal** and should **not be indication for cesarean delivery**.
  - Main abnormality is **arrest of active phase** (reserve this diagnosis for women ≥6 cm of dilation with ruptured membranes who show no cervical change despite **4 h of adequate uterine activity** or **≥6 h of oxytocin administration with inadequate uterine activity**).

Stage 2 begins with complete cervical dilation and ends with delivery of the fetus. Its **purpose** is **descent of the fetus** through the birth canal.

- Whereas in stage 1 **uterine contractions** are the only force that acts on cervical dilation, in stage 2 **maternal pushing efforts** are vitally important to augment the uterine contractions to bring about descent of the fetal presenting part.
- No absolute maximum length of time spent in stage 2 of labor, after which all women should undergo operative delivery, has been identified.
- Main abnormality is **prolonged second stage**.
- **Duration of stage 2** may be up to 3 h in a primipara (4 h with epidural) or 2 h in a multipara (3 h with epidural).

Stage 3 begins with delivery of the fetus and ends with expulsion of the placenta. The mechanism of placental separation from the uterine wall is dependent on myometrial contractions shearing off the anchoring villi. This is usually augmented with IV oxytocin infusion.

- **Signs of stage 3** include gush of blood vaginally, change of the uterus from long to globular, or "lengthening" of the umbilical cord
- **Duration** may be up to 30 minutes in all women.
- Main abnormality is **prolonged third stage**.

Stage 4 is not an official stage of labor but rather a critical 2 h period of close observation of the parturient immediately after delivery. Vital signs and vaginal bleeding are monitored to recognize and promptly treat preeclampsia and postpartum hemorrhage.

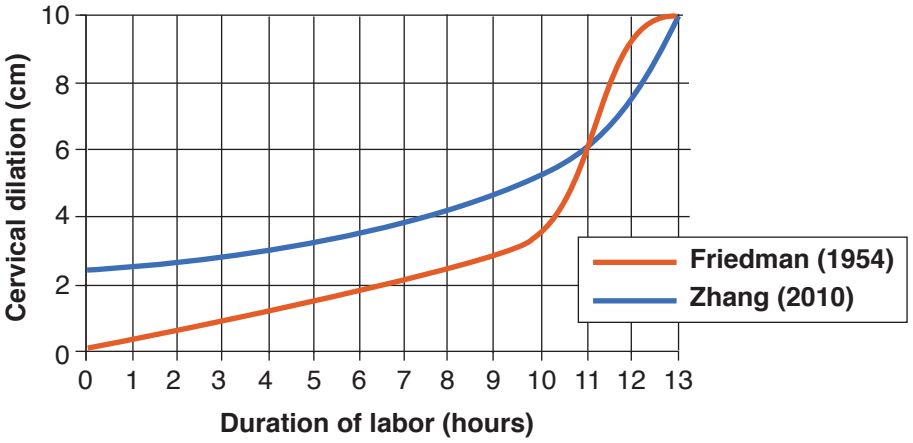


Figure I-14-1. Old versus New Labor Curves

CONDUCT OF NORMAL SPONTANEOUS LABOR

A 20-year-old primigravida comes to the maternity unit at 39 weeks' gestation complaining of regular uterine contractions every 3 min for the past 6 h. The contractions are becoming more frequent. She denies any vaginal fluid leakage. Vital signs are blood pressure 125/75 mm Hg, pulse 80 beats/min, respirations 17 breaths/min. On pelvic examination the fetus is cephalic presentation at –1 station. The cervix is 5 cm dilated, 90% effaced, and soft and anterior in position. On the electronic fetal monitor (EFM) the fetal heart rate baseline is 135 beats/min with moderate variability, frequent accelerations, and no decelerations. How will you manage this patient?

Preadmission

The parturient is not admitted to the maternity unit until cervical dilation is at least 4–5 cm, unless premature membrane rupture has occurred. Fetal presentation is confirmed to be cephalic.

Admission

On admission intravenous access is established, and oral clear liquid may be ingested. The patient is allowed whatever position is comfortable; however, the lateral recumbent position is encouraged as it optimizes uteroplacental blood flow.

First Stage

The fetal heart rate is assessed, usually with continuous electronic monitoring. Cervical dilation and fetal head descent are followed through appropriately spaced vaginal examinations. Amniotomy is performed in the active phase when the fetal head is well applied to the cervix. Obstetric analgesia is administered at patient request.

Second and Third Stages

Maternal pushing efforts augment uterine contractions in the second stage of labor. An episiotomy is not routine but is performed as indicated. After delivery of the fetus, the placenta is allowed to spontaneously separate, after which IV oxytocin is administered to prevent uterine atony and bleeding.

Recovery Period

For the first 2 hours postpartum, the parturient is observed closely for excessive bleeding and development of preeclampsia.

ABNORMAL LABOR

Prolonged Latent Phase

> A 29-year-old multigravida at 40 weeks' gestation is being observed in the maternity unit. She states she has been having regular uterine contractions for 24 h but cervical dilation remains at 1–2 cm. Her vital signs are stable. EFM tracing is reassuring regarding fetal status.

Diagnosis. Prolonged latent phase requires that, in the face of regular uterine contractions, the cervical dilation is <6 cm for a duration of >20 h in a primipara or >14 h in a multipara.

Cause. Latent-phase abnormalities are most commonly caused by injudicious analgesia. Other causes are contractions, which are hypotonic (inadequate frequency, duration, or intensity) or hypertonic (high intensity but inadequate duration or frequency).

Management. This involves (a) therapeutic rest with narcotics or sedatives, (b) oxytocin administration, or (c) amniotomy. Cesarean delivery is never appropriate management for prolonged latent phase.

OB Triad

Prolonged Latent Phase

- Pregnant with regular uterine contractions
- Cervix dilated 2 cm
- No cervical change in 14 h

Arrested Active Phase

High-Yield

> A 22-year-old primigravida at 39 weeks' gestation has progressed in labor to 8 cm of cervical dilation but has not changed for 3 h. Her vital signs are stable. EFM tracing is reassuring regarding fetal status.

Diagnosis. Arrested active phase is diagnosed if membranes are ruptured and cervical dilation has not changed for (a) ≥ 4 h with adequate uterine contractions or (b) ≥ 6 h of IV oxytocin administration with inadequate uterine contractions.

Causes. Active-phase abnormalities may be caused by either abnormalities of the **passenger** (excessive fetal size or abnormal fetal orientation in the uterus), abnormalities of the **pelvis** (bony pelvis size), or abnormalities of **powers** (dysfunctional or inadequate uterine contractions).

OB Triad

Active Phase Arrest

- Pregnant with regular uterine contractions
- Cervix dilated 8 cm
- No cervical change in 4 h

Management. This is directed at assessment of uterine contraction quality. Contractions should occur every 2–3 min and last 45–60 s with 50 mm Hg intensity. If contractions are hypotonic, IV oxytocin is administered. If contractions are hypertonic, give morphine sedation. If contractions are adequate, proceed to emergency cesarean section.

OB Triad

Second-Stage Arrest

- Pregnant with regular uterine contractions
- 10 cm dilation at +1 station
- No descent change in 3 h

Prolonged Second Stage

High-Yield

A 20-year-old primigravida at 41 weeks' gestation has progressed in labor to 10 cm of cervical dilation and has been pushing for the past 3 h. The fetus is cephalic presentation, right occiput transverse position. The fetal head has not descended below +2 station. Her vital signs are stable. EFM tracing is reassuring regarding fetal status.

Diagnosis.

- **Nulliparous** women: After complete dilation, no progress in either **descent or rotation** of the fetus after ≥3 h without epidural anesthesia and ≥4 h with epidural anesthesia.
- **Multiparous** women: After complete dilation, no progress in either **descent or rotation** of the fetus after ≥2 h without epidural anesthesia and ≥3 h with epidural anesthesia.

Management. This involves assessment of uterine contractions and maternal pushing efforts. IV oxytocin can strengthen the contractions. Enhanced coaching to optimize maternal pushing should be utilized as needed. If they are both adequate, assess whether the fetal head is engaged. If the head is not engaged, proceed to emergency cesarean. If the head is engaged, consider a trial of either obstetric forceps or a vacuum extractor delivery.

Prolonged Third Stage

High-Yield

A 20-year-old primigravida at 39 weeks' gestation underwent a spontaneous vaginal delivery 40 min ago of a healthy 3,500 g daughter. However, the placenta has still not delivered. Her vital signs are stable.

Diagnosis. Failure to deliver the placenta within 30 minutes.

Cause. May be inadequate uterine contractions. If the placenta does not separate in spite of IV oxytocin stimulation of myometrium contractions, think of abnormal placental implantation (e.g., placenta **accreta**, placenta **increta**, and placenta **percreta**).

Management. May require manual placental removal or rarely even hysterectomy.

OBSTETRIC COMPLICATIONS DURING LABOR

Prolapsed Umbilical Cord

High-Yield

A 34-year-old multigravida with a known uterine septum comes to the maternity unit at 34 weeks' gestation complaining of regular uterine contractions. She underwent a previous cesarean at 37 weeks' gestation for breech presentation. Pelvic examination determines that the fetus is a footling breech. Her cervix is 6 cm dilated with bulging membranes. During the examination, the patient's bag of waters suddenly ruptures, and a loop of umbilical cord protrudes through the cervix between the fetal extremities.

Umbilical cord prolapse is an obstetric emergency because if the cord gets compressed, fetal oxygenation will be jeopardized, with potential fetal death.

Prolapse can be **occult** (the cord has not come through the cervix but is being compressed between the fetal head and the uterine wall), partial (the cord is between the head and the dilated cervical os but has not protruded into the vagina), or **complete** (the cord has protruded into the vagina).

Risk Factors. Rupture of membranes with the presenting fetal part not applied firmly to the cervix, malpresentation.

Management. Do not hold the cord or try to push it back into the uterus. Place the patient in knee-chest position, elevate the presenting part, avoid palpating the cord, and perform immediate cesarean delivery.

OB Triad

Prolapsed Umbilical Cord

- Pregnant with regular uterine contractions
- Amniotomy at –2 station
- Severe variable decelerations

Shoulder Dystocia

High-Yield

A 20-year-old primigravida at 39 weeks' gestation was pushing in the second stage of labor for 90 min and has just delivered the fetal head. However, in spite of vigorous pushing efforts by the mother and moderate traction on the fetal head, you are unable to deliver the anterior shoulder. Since delivery of the fetal head, 30 s has passed. The fetal heart rate is now 70 beats/min.

Diagnosis. This diagnosis is made when delivery of the fetal shoulders is delayed after delivery of the head. It is usually associated with fetal shoulders in the anterior-posterior plane, with the anterior shoulder impacted behind the pubic symphysis. It occurs in 1% of deliveries and may result in permanent neonatal neurologic damage in 2% of cases.

Risk Factors. Include **maternal diabetes**, obesity, and postdates pregnancy, which are associated with fetal macrosomia. Even though incidence increases with birth weight, half of shoulder dystocias occur in fetuses <4,000 grams.

Management. Includes suprapubic pressure, maternal thigh flexion (McRobert's maneuver), internal rotation of the fetal shoulders to the oblique plane (Wood's "corkscrew" maneuver), manual delivery of the posterior arm, and Zavanelli maneuver (cephalic replacement).

OB Triad

Shoulder Dystocia

- Second stage of labor
- Head has delivered
- No further delivery of body

Obstetric Lacerations

Perineal lacerations are classified by the extent of tissue disruption between the vaginal introitus and the anus.

- **First degree:** involve only the vaginal mucosa. Suture repair is often not needed
- **Second degree:** involve the vagina and the muscles of the perineal body but do not involve the anal sphincter; suturing is necessary
- **Third degree:** involve the vagina, the perineal body, and the anal sphincter but not the rectal mucosa; suturing is necessary to avoid anal incontinence
- **Fourth degree:** involve all the way from the vagina through to the rectal mucosa; complications of faulty repair or healing include rectovaginal fistula

Episiotomy

This is a surgical incision made in the perineum to enlarge the vaginal opening and assist in childbirth. It is one of the most common female surgical procedures. American-trained physicians tend to prefer a midline episiotomy whereas British-trained physicians tend to perform mediolateral episiotomies. It is not practiced routinely in the United States today because the arguments made in its favor **have not been shown** to have scientific support.

- **False arguments:** less perineal pain; more rapid return of sexual activity; less urinary incontinence; less pelvic prolapse
- **Disadvantages:** more perineal pain than with lacerations; longer return to sexual activity; more extensions into the anal sphincter and rectum
- **Possible indications:** shoulder dystocia, non-reassuring fetal monitor tracing, forceps or vacuum extractor vaginal delivery, vaginal breech delivery, narrow birth canal

Obstetric Anesthesia 15

Learning Objectives

- ❏ Differentiate the physiology of anesthesia as applied to a pregnant versus a non-pregnant woman
- ❏ Describe possible anesthetic complications and management strategies

PHYSIOLOGY

Pain relief from uterine contractions and cervical dilation in **stage 1 of labor** involves thoracic nerve roots, T10 to T12. Pain relief from perineal distention in **stage 2 of labor** involves sacral nerve roots, S2 to S4.

- Pregnancy predisposes to hypoxia because of decreased functional residual capacity.
- Placental transfer of medications exposes the fetus to lipid-soluble anionic substances.
- Antacids should be given prophylactically because of delayed gastric emptying time in pregnancy.
- Uterus should be laterally displaced to avoid inferior vena cava compression in the supine position.

ANESTHETIC OPTIONS DURING LABOR

Intravenous agents include sedatives, which are frequently given in the active phase of labor. **Advantages** include ease of administration and inexpensive cost. **Disadvantages** include neonatal depression if given close to delivery. The neonate may need administration of **naloxone** to reverse the effect.

Paracervical block is a mode of conduction anesthesia that involves bilateral transvaginal local anesthetic injection to block **Frankenhauser' ganglion** lateral to the cervix. It is administered in the active phase of labor. **Disadvantages** include temporary high levels of local anesthetic in the uterus that may lead to **transitory fetal bradycardia**, which is managed conservatively.

Pudendal block is a mode of conduction anesthesia that involves bilateral transvaginal local anesthetic injection to block the pudendal nerve as it passes by the ischial spines. It is administered in stage 2 of labor to provide perineal anesthesia.

OB Triad

Paracervical Block Effect

- Term pregnancy in active labor
- Local anesthetic injection into cervix
- Immediate fetal bradycardia

OB Triad

Epidural Block Side Effect

- Pregnancy in active labor
- Conduction anesthesia given
- ½ body numb; ½ body pain

OB Triad

High Spinal (Intrathecal)

- Pregnancy in active labor
- Conduction anesthesia given
- Patient stops breathing

Epidural block is a mode of conduction anesthesia that involves injection of local anesthetic into the epidural space to block the lumbosacral nerve roots during both stages 1 and 2 of labor. **Advantages** include use for either vaginal delivery or cesarean section. **Disadvantages** include patchy block from nonuniform spread of the local anesthetic around the nerve roots. **Complications** include hypotension from peripheral vascular dilation owing to sympathetic blockade and spinal headache from inadvertent dural puncture, as well as CNS bleeding or infection (rare). Hypotension is treated with IV fluids and IV ephedrine. Spinal headache is treated with IV hydration, caffeine, or blood patch.

Spinal block is a mode of conduction anesthesia that involves injection of local anesthetic into the subarachnoid space to block the lumbosacral nerve roots. It is used as a saddle block for stage 2 of labor and for cesarean delivery. **Advantages** are complete predictable anesthesia. **Complications** include hypotension from peripheral vascular dilation because of sympathetic blockade (common) and spinal headache (rare), as well as CNS bleeding or infection (rare).

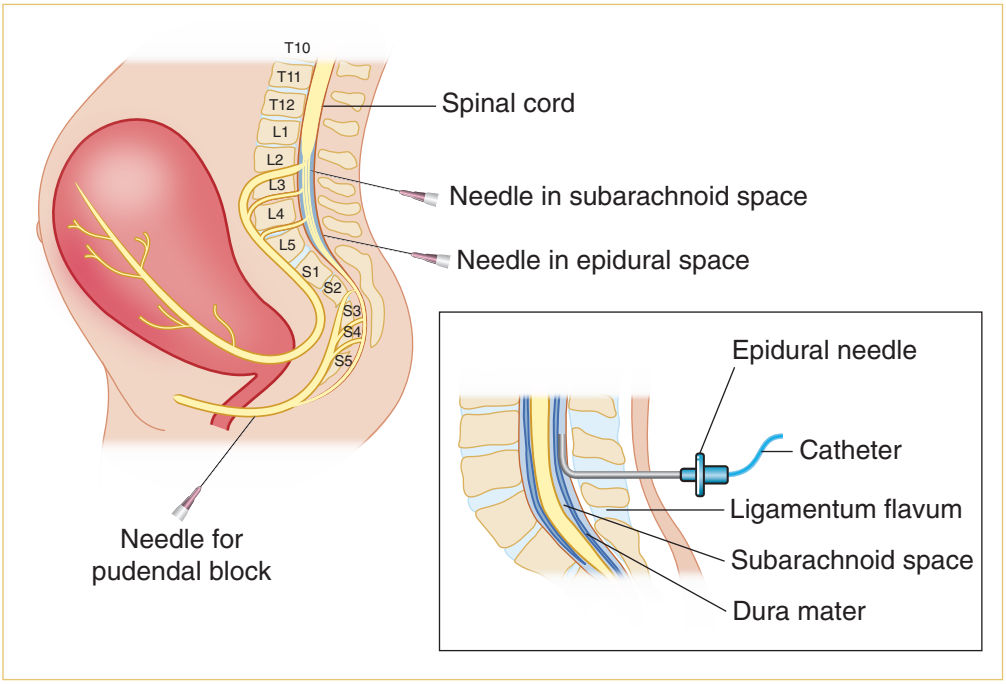


Figure I-15-1. Anesthetic Options During Labor

General anesthesia is seldom used for vaginal delivery and rarely for cesarean section. **Indications** include need for rapid emergency delivery and maternal medical conditions in which conduction anesthesia is unsafe (e.g., blood dyscrasia, thrombocytopenia). **Complications** include aspiration pneumonia, atelectasis, and uterine atony (associated with inhalation agents, e.g., halothane, enflurane).

Intrapartum Fetal Monitoring 16

Learning Objectives

- ❑ Describe the appropriate use of intrapartum fetal monitoring including FHR monitoring, fetal pH assessment, and category III fetal monitoring tracings
- ❑ Describe intrauterine resuscitation

FETAL HEART RATE MONITORING

Normal fetal heart rate (FHR) findings are highly reassuring of fetal well-being. Abnormal FHR findings are poor predictors of fetal compromise. Wide usage of electronic FHR monitoring has not lowered the rate of cerebral palsy (CP) because the antecedents of CP appear not to be intrapartum events, but rather antenatal events. The false-positive rate for electronic FHR monitoring for predicting CP is >99%.

Both of the following modalities are equivalent in predicting fetal outcome.

- **Intermittent auscultation** of FHR is performed with a fetoscope using auditory FHR counting averaged for 10–15 s.
- **Electronic monitoring** measures the milliseconds between consecutive cardiac cycles giving an instantaneous FHR continuously.

External Devices

High-Yield

External devices (**most common**) are placed on the uterine fundus. **Advantages** are utilization before significant cervical dilation and membrane rupture. **Disadvantages** are poor quality tracing with maternal obesity and maternal discomfort from the device belts.

- **Fetal.** A continuous ultrasound transducer picks up fetal cardiac motion but also can register maternal great vessel pulsations.
- **Contractions.** A tocographic transducer device senses the change in uterine wall muscle tone. It can measure the beginning and ending of contractions but cannot assess contraction intensity.

Internal Devices

High-Yield

Internal devices are placed through the dilated cervix. **Advantages** include optimum signal quality, which is unaffected by maternal obesity. **Disadvantages** include limitation to labor when cervical dilation and membrane rupture have occurred.

- **Fetal.** A direct scalp electrode precisely senses each QRS complex of the fetal cardiac cycle. Complications can include fetal scalp trauma and infection.
- **Contractions.** An intrauterine pressure catheter (IUPC) placed into the uterine cavity precisely registers intrauterine hydrostatic changes with each contraction.

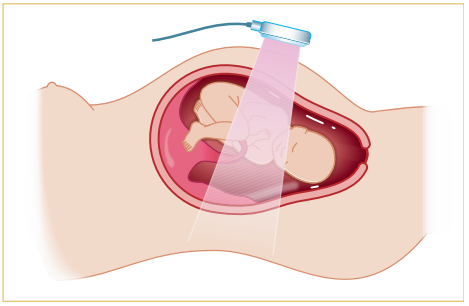


Figure I-16-1. Electronic Fetal Heart Rate Monitor

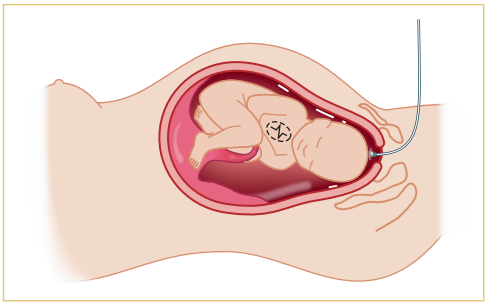


Figure I-16-2. Internal Fetal Heart Rate Monitor

INTRAPARTUM FETAL HEART RATE MONITORING

Definitions

High-Yield

Baseline Fetal Heart Rate (FHR): The mean FHR rounded to increments of 5 beats/min during a 10-minute segment. Normal FHR baseline is 110–160 beats/minute.

Tachycardia: FHR baseline is >160 beats/min.

- Non-hypoxic explanations include:
  - **Maternal:** medications (β-adrenergic agonists [terbutaline], atropine, scopolamine), fever, thyrotoxicosis
  - **Fetal:** repetitive accelerations (from fetal movements), fetal tachyarrhythmias, prematurity

Bradycardia: FHR baseline is <110 beats/min.

- Non-hypoxic explanations include:
  - **Maternal medications:** β-adrenergic blockers, local anesthetics
  - **Fetal arrhythmia:** congenital heart block (associated with maternal lupus)

Baseline variability describes fluctuations in the baseline FHR that are irregular in amplitude and frequency. It is a reflection of the autonomic interplay between the sympathetic and parasympathetic nervous system.

- **Absent** amplitude range undetectable
- **Minimal** amplitude range detectable but ≤5 beats/min
- **Moderate** (normal): amplitude range 6–25 beats/min
- **Marked:** amplitude range >25 beats/min

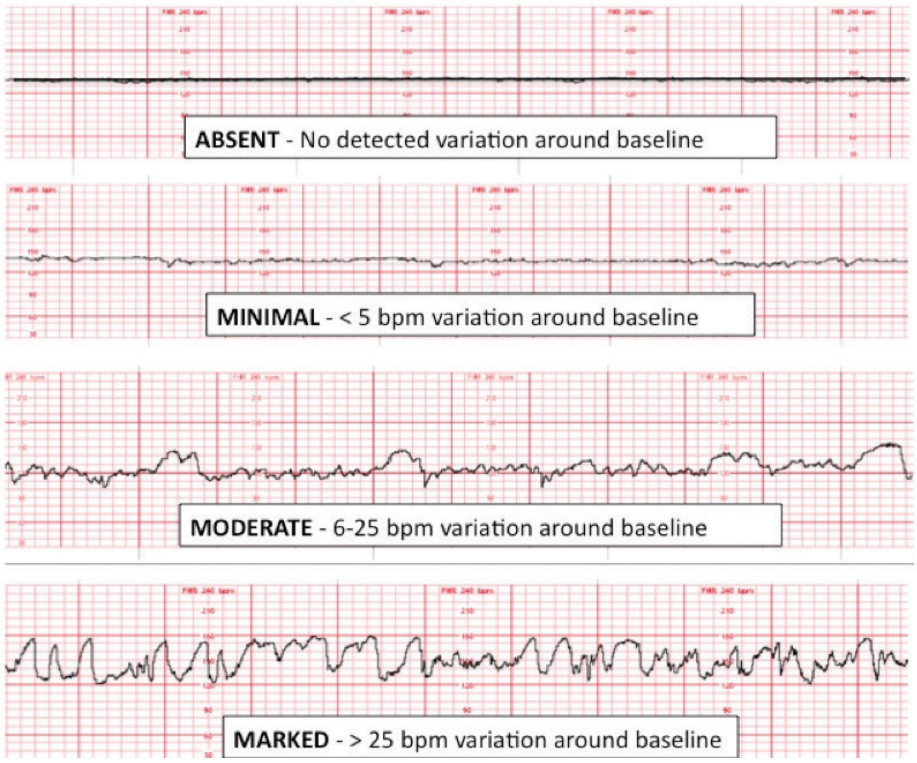


Figure I-16-3. Fetal Heart Rate Baseline Variability

Acceleration: A visually apparent **abrupt** increase (onset to peak in <30 seconds) in the FHR. These are mediated by the sympathetic nervous system in response to fetal movements or **scalp stimulation**.

- **At ≥32 weeks gestation,** an acceleration has a peak of >15 beats/min above baseline, with a duration of >15 seconds but <2 min from onset to return.
- **At <32 weeks gestation**, an acceleration has a peak of ≥10 beats/min above baseline, with a duration of ≥10 sec but <2 min from onset to return.

OB Triad

Early Decelerations

- Gradual drop of FHR
- Gradual return of FHR
- Mirror image of contraction

OB Triad

Late Decelerations

- Gradual drop of FHR
- Gradual return of FHR
- Delayed in relation to contractions

OB Triad

Variable Decelerations

- Abrupt drop of FHR
- Sudden return of FHR
- Variable in relation to contractions

Early deceleration: A visually apparent usually symmetrical **gradual** decrease and return of the FHR associated with a uterine contraction. These are mediated by parasympathetic stimulation and occur in response to **head compression**.

- A gradual FHR decrease is defined as from the onset to the FHR nadir of ≥30 seconds.
- The decrease in FHR is calculated from the onset to the nadir of the deceleration.
- The nadir of the deceleration occurs at the same time as the peak of the contraction.

Late deceleration: A visually apparent usually symmetrical **gradual** decrease and return of the FHR associated with a uterine contraction. These are mediated by either vagal stimulation or myocardial depression and occur in response to **placental insufficiency**.

- A gradual FHR decrease is defined as from the onset to the FHR nadir of ≥30 seconds.
- The decrease in FHR is calculated from the onset to the nadir of the deceleration.
- The deceleration is delayed in timing, with the nadir of the deceleration occurring after the peak of the contraction.

Variable deceleration: A visually apparent **abrupt** decrease in FHR. These are mediated by **umbilical cord compression.**

- An abrupt FHR decrease is defined as from the onset of the deceleration to the beginning of the FHR nadir of <30 seconds.
- The decrease in FHR is calculated from the onset to the nadir of the deceleration.
- The decrease in FHR is ≥15 beats per minute, lasting ≥15 seconds, and <2 minutes in duration.

Sinusoidal pattern: A visually apparent, smooth, sine wave-like undulating pattern in FHR baseline with a cycle frequency of 3–5/min which persists for ≥20 min.

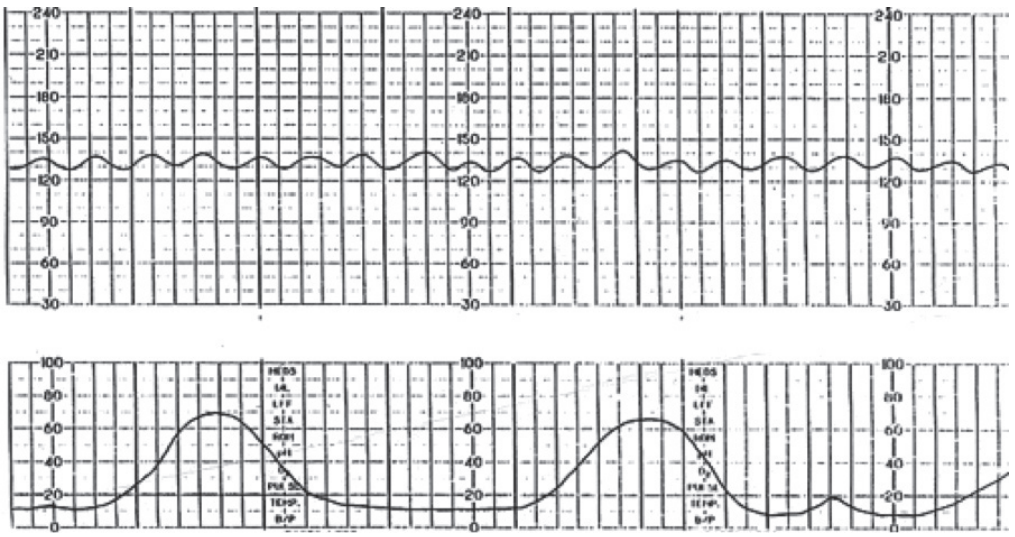


Figure I-16-4. Sinusoidal Fetal Heart Rate Pattern

Fetal Heart Rate Categories

High-Yield

A **three-tiered system** for the categorization of FHR patterns is recommended. Categorization evaluates the fetus at that point in time; tracing patterns can and will change. FHR tracing may move back and forth between the categories depending on the clinical situation and management strategies used.

Category I: FHR tracings are normal

Criteria include all of the following:

- **Baseline rate:** 110–160 beats/min
- **Baseline FHR variability:** moderate
- **Late or variable decelerations:** absent
- **Early decelerations:** present or absent
- **Accelerations:** present or absent

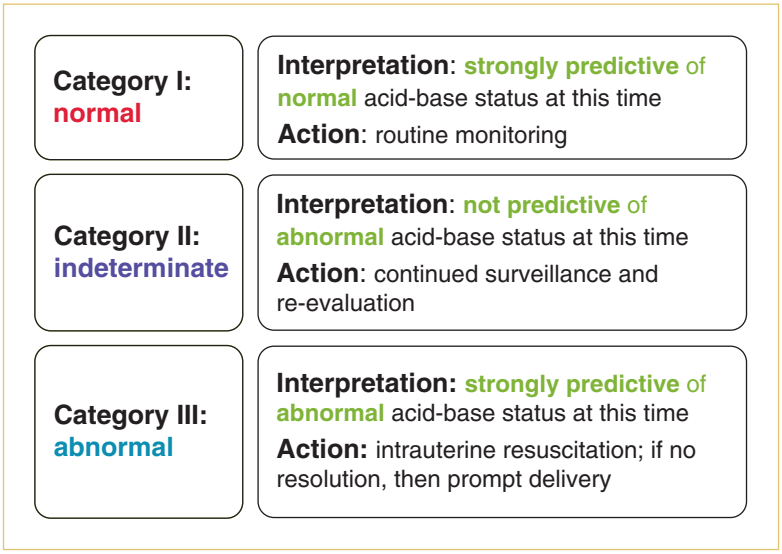
Category II: FHR tracings are indeterminate

These include all FHR tracings not categorized as category I or III and may represent an appreciable fraction of those encountered in clinical care.

Category III: FHR tracings are abnormal

Criteria include absent baseline FHR variability and any of the following:

- Recurrent late decelerations
- Recurrent variable decelerations
- Bradycardia
- Sinusoidal pattern



Used with permission: Elmar Sakala, MD

Figure I-16-5. Categorization of FHR Patterns

Note

Remember, FHR tracing patterns provide information only on the current acid–base status of the fetus.

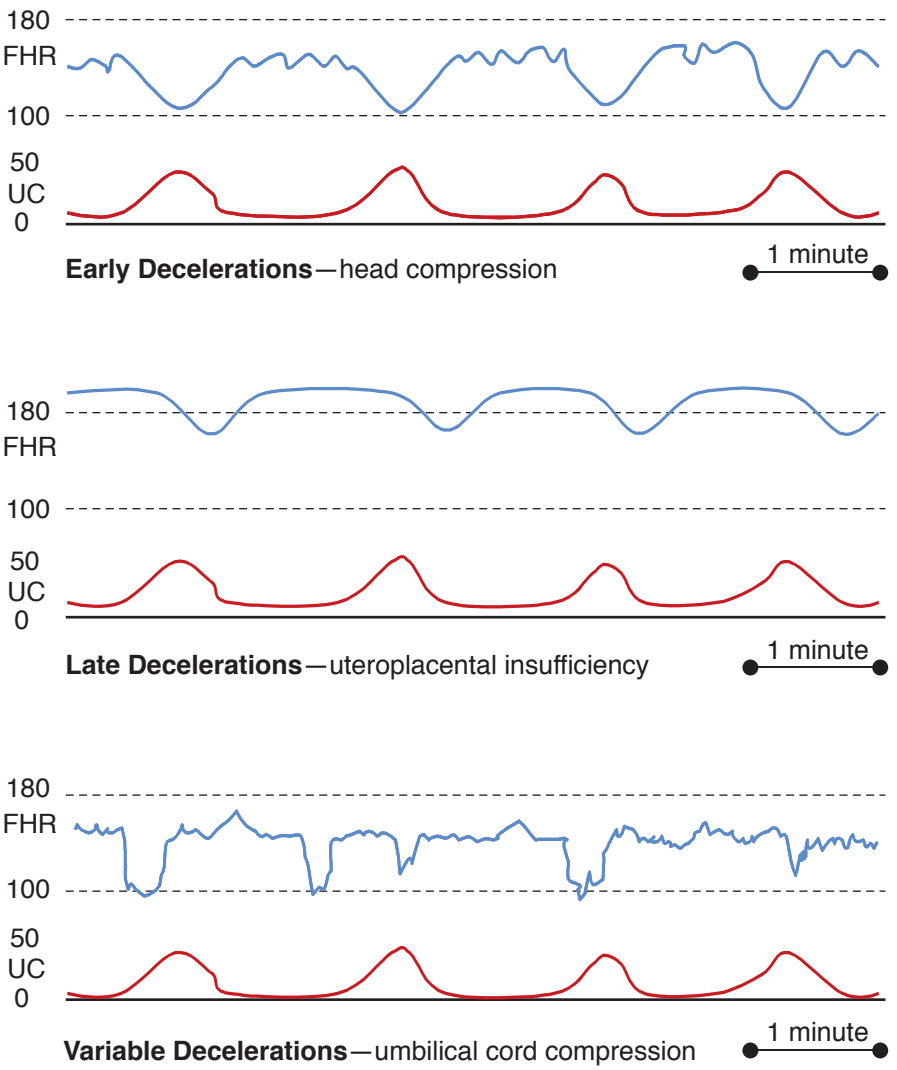


Figure I-16-6. Electronic Fetal Monitor Decelerations

INTRAUTERINE FETAL RESUSCITATION

Decrease uterine contractions: Turn off any IV oxytocin infusion or administer terbutaline 0.25 mg subcutaneously to enhance intervillous placental blood flow.

Augment IV fluid volume: Infuse the parturient with a 500 mL bolus of intravenous normal saline rapidly to enhance uteroplacental infusion.

Administer high-flow oxygen: Give the parturient 8–10 L of oxygen by facemask to increase delivery of maternal oxygen to the placenta.

Amnioinfusion is useful for eliminating or reducing the severity of variable decelerations.

Change maternal position: Removing the parturient from the supine position decreases inferior vena cava compression and enhances cardiac return, thus cardiac output to the placenta. Turning the parturient from one lateral position to the other may relieve any umbilical cord compression that may be present.

Vaginal examination: Perform a digital vaginal examination to rule out possible prolapsed umbilical cord.

Fetal scalp stimulation: Perform a digital scalp stimulation observing for accelerations, which would be reassuring of fetal condition.

FETAL pH ASSESSMENT

Intrapartum: Fetal scalp blood pH may be used in labor if the EFM strip is equivocal. Prerequisites include cervical dilation, ruptured membranes, and adequate descent of the fetal head. Contraindications are suspected fetal blood dyscrasia. A small, shallow fetal scalp incision is made resulting in capillary bleeding. The blood is collected in a heparinized capillary tube and sent to the laboratory for blood gas analysis. Normal fetal pH is $\geq$7.20. This procedure is seldom performed today.

Postpartum: Umbilical cord blood pH is used to confirm fetal status at delivery. It involves obtaining both umbilical cord venous and arterial samples. Arterial Pco_2 and base deficit values are higher than venous, but pH and Po_2 are lower. Normal fetal arterial pH is $\geq$7.20.

CATEGORY III: ABNORMAL TRACINGS

> A 20-year-old primigravida at 39 weeks' gestation is in active labor at 7 cm of cervical dilation. The EFM strip shows a baseline heart rate of 175 beats/min, and variability is absent, but repetitive late decelerations are seen after each contraction. No accelerations are noted.

Recognize that most abnormal tracings are not caused by fetal hypoxia. Ask whether the tracing has biologic plausibility.

- **Examine the EFM strip carefully** looking for baseline heart rate, degree of variability, and presence of periodic changes (accelerations, decelerations).
- **Confirm abnormal findings** using criteria discussed above (category II or III).
- **Identify nonhypoxic causes** present that could explain the abnormal findings.
- **Initiate the intrauterine resuscitation measures** described previously to enhance placental perfusion and fetal oxygenation.
- **Observe for normalization** of the EFM tracing.
- Prepare for delivery promptly if resuscitation measures do not normalize EFM tracing.

Specific interventions if immediate delivery Is indicated:

- In stage 1 of labor, the only option is emergency cesarean section.
- In stage 2 of labor, an operative vaginal delivery (e.g., vacuum extractor assisted or obstetrical forceps) may be appropriate, or an emergency cesarean section must be performed.

Operative Obstetrics 17

Learning Objective

- ❑ Describe the risks and indications for the use of obstetric forceps, vacuum extractor, emergency cesarean section, and elective cesarean section

OPERATIVE OBSTETRICS

Operative obstetrics refers to any method used to deliver the fetus other than uterine contractions and maternal pushing efforts. It may include vaginal or cesarean routes.

Forceps

Obstetric forceps are metal instruments used to provide traction, rotation, or both to the fetal head. Classification for use is as follows:

- **Outlet** (**most common** forceps use): fetal head is on pelvic floor
- **Low:** fetal head is below +2 station but has not reached the pelvic floor
- **Mid** (seldom used today): fetal head is below 0 station but has not reached +2 station
- **High** (never appropriate in modern obstetrics because of risk to both mother and fetus): fetal head is unengaged, above 0 station

Indications are as follows:

- **Prolonged second stage** (**most common indication** for forceps): may be because of dysfunctional labor or suboptimal fetal head orientation
- **Category III EFM strip:** fetal heart rate monitor pattern suggests fetus is not tolerating labor
- **Avoid maternal pushing:** include various conditions in which pushing efforts may be hazardous to parturient, e.g., cardiac, pulmonary, or neurologic disorders
- **Breech presentation:** shorten the time to deliver the head of a vaginal breech fetus

Prerequisites include the following:

- Clinically adequate pelvic dimensions
- Experienced operator
- Full cervical dilation
- Engaged fetal head
- Orientation of fetal head certain

Complications can include lacerations to the vagina, cervix, perineum, and uterus (**maternal**); and soft-tissue compression or cranial injury caused by incorrectly placed forceps blades (**fetal-neonatal**).

Vacuum Extractor

A vacuum extractor is a cuplike instrument that is held against the fetal head with suction. Traction is thus applied to the fetal scalp, which along with maternal pushing efforts results in descent of the head leading to vaginal delivery. The cups may be metal or plastic, rigid or soft.

A vacuum extractor has some **advantages** over forceps.

- **Fetal head orientation:** Precise knowledge of fetal head position and attitude is not essential.
- **Space required:** The vacuum extractor does not occupy space adjacent to the fetal head.
- **Perineal trauma:** Third- and fourth-degree lacerations are fewer.
- **Head rotation:** Fetal head rotation occurs spontaneously at the station best suited to fetal head configuration and maternal pelvis.

A vacuum extractor also has some **disadvantages** over forceps.

- **Cup pop-offs:** Excessive traction can lead to sudden decompression as the cup suction is released.
- **Scalp trauma:** Scalp skin injury and lacerations are common.
- **Subgaleal hemorrhage and intracranial bleeding** are rare.
- **Neonatal jaundice** arises from scalp bleeding.

The **indications** for a vacuum extractor are similar to those of forceps.

- **Prolonged second stage:** This may be because of dysfunctional labor or suboptimal fetal head orientation.
- **Nonreassuring EFM strip:** The FHR monitor pattern suggests the fetus is not tolerating labor.
- **Avoid maternal pushing:** These include various conditions in which pushing efforts may be hazardous to the parturient, e.g., cardiac, pulmonary, or neurologic disorders.

Prerequisites for vacuum extractor use include:

- Clinically adequate pelvic dimension
- Experienced operator
- Full cervical dilation
- Engaged fetal head
- Gestational age ≥34 weeks

Complications can include vaginal lacerations from entrapment of vaginal mucosa between the suction cup and fetal head (**maternal**), neonatal **cephalohematoma** and scalp lacerations (common), and life-threatening complications of **subgaleal hematoma** or **intracranial hemorrhage** (uncommon but associated with vacuum duration >10 min) (**neonatal**).

Cesarean Section

High-Yield

Cesarean section is a procedure in which the fetus is delivered through incisions in the maternal anterior abdominal and uterine walls. The overall U.S. cesarean section rate in 2011 was ~33% (includes both primary and repeat procedures).

Risks. Maternal mortality and morbidity are higher than with vaginal delivery, especially with emergency cesareans performed in labor. Maternal mortality is largely anesthetic-related, with overall mortality ratio of 25 per 100,000.

- **Hemorrhage:** Blood loss is 2× that of a vaginal delivery, with mean of 1,000 mL.
- **Infection:** Sites of infection include endometrium, abdominal wall wound, pelvis, urinary tract, or lungs. Prophylactic antibiotics can decrease infectious morbidity.
- **Visceral injury:** Surrounding structures can be injured (e.g., bowel, bladder, and ureters).
- **Thrombosis:** Deep venous thrombosis is increased in the pelvic and lower extremity veins.

Uterine Incisions

- **Low segment transverse.** This incision is made in the noncontractile portion of the uterus and is the one most commonly used. The bladder must be dissected off the lower uterine segment. It has a low chance of uterine rupture in subsequent labor (0.5%).
  - **Advantages** are trial of labor in a subsequent pregnancy is safe; the risk of bleeding and adhesions is less.
  - **Disadvantages** are the fetus(es) must be in longitudinal lie; the lower segment must be developed.
- **Classical.** This incision is made in the contractile fundus of the uterus and is less commonly performed. Technically it is easy to perform, and no bladder dissection is needed. Risk of uterine rupture both before labor as well as in subsequent labor is significant (5%). Repeat cesarean should be scheduled before labor onset.
  - **Advantages** are any fetus(es) regardless of intrauterine orientation can be delivered; lower segment varicosities or myomas can be bypassed.
  - **Disadvantages** are trial of labor in a subsequent pregnancy is unsafe; the risk of bleeding and adhesions is higher.

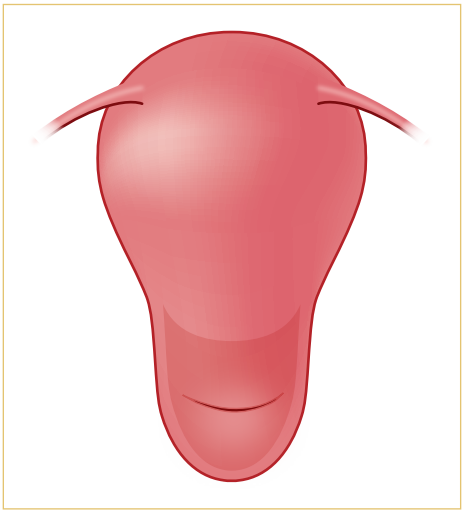


Figure I-17-1. Low Segment Transverse Incision

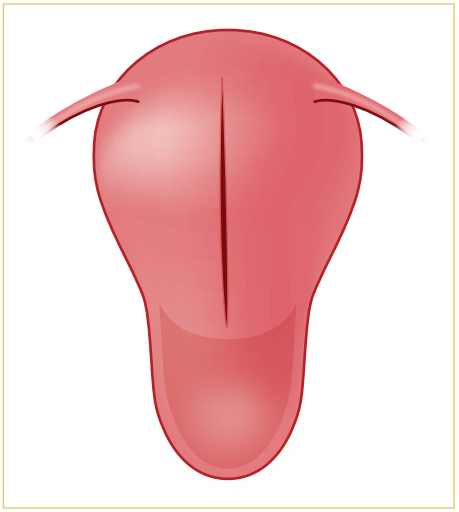


Figure I-17-2. Classical Uterine Incision

OB Triad

Low Transverse Uterine Incision

- Low risk of rupture (0.5% in labor)
- Less blood loss and adhesions
- Safe for subsequent labor trial

OB Triad

Classical Uterine Incision

- High risk of rupture (5% in labor)
- More blood loss and adhesions
- Risky for subsequent labor trial

Indications for primary cesarean section include the following:

- **Cephalopelvic disproportion (CPD)** (**most common** indication for cesarean delivery): This term literally means the pelvis is too small for the fetal head. In actual practice, it most commonly indicates failure of the adequate progress in labor, which may be related to dysfunctional labor or suboptimal fetal head orientation.
- **Fetal malpresentation:** This refers most commonly to breech presentation, but also means any fetal orientation other than cephalic.
- **Category III EFM strip:** The FHR monitor pattern suggests the fetus may not be tolerating labor, but commonly this is a false-positive finding.

Elective Cesarean on Maternal Request

The U.S. National Institutes of Health (NIH) held a consensus conference in March 2006 to determine the scientific basis for maternal and fetal risks and benefits to cesarean delivery on maternal request (CDMR). After two days of presentations by experts in the field and input from the audience, the consensus was that "the available information comparing the risks and benefits of CDMR versus planned vaginal birth do not provide the basis for a recommendation in either direction."

Recommendations from the independent panel of experts include:

- Women should be counseled individually for risks and benefits.
- Women who are considering having >2 children should be aware that a cesarean section causes uterine scarring; these women should avoid a primary cesarean section.
- Women should not have a cesarean section prior to 39 weeks' gestation.

VAGINAL BIRTH AFTER CESAREAN (VBAC)

Successful vaginal delivery rate is up to 80% in carefully selected patients. **Criteria** for trial of labor include patient consent, nonrepetitive cesarean indication (e.g., breech, placentae previa), previous low segment transverse uterine incision, and clinically adequate pelvis.

EXTERNAL CEPHALIC VERSION

External cephalic version consists of externally manipulating the gravid abdomen without anesthesia to turn the fetus from transverse lie or breech presentation. The optimum time for version is 37 weeks' gestation, and success rates are 60–70%.

Potential hazards are umbilical cord compression or placental abruption requiring emergency cesarean section.

Postpartum Issues 18

Learning Objectives

- ❑ Describe the causes and management of postpartum hemorrhage and fever
- ❑ List the sequence of physiologic changes expected after delivery
- ❑ Provide an overview of the special considerations for immunizations and contraception postpartum

POSTPARTUM PHYSIOLOGIC ISSUES

Reproductive Tract Changes

- **Lochia:** It is composed of superficial layers of the endometrial decidua that are shed through the vagina during the first three postpartum weeks. For the first few days the color is red (**lochia rubra**), changing during the next week to pinkish (**lochia serosa**), ending with a whitish color (**lochia alba**) by the end of the second week.
- **Cramping:** The myometrial contractions after delivery constrict the uterine venous sinuses, thus preventing hemorrhage. These lower midline cramps may be painful and are managed with mild analgesics.
- **Perineal Pain:** Discomfort from an episiotomy or perineal lacerations can be minimized in the first 24 hours with ice packs to decrease the inflammatory response edema. A heat lamp or sitz bath is more helpful after the first day to help mobilize tissue fluids.

Urinary Tract Changes

- **Hypotonic Bladder:** Intrapartum bladder trauma can result in increased post-void residual volumes. If the residuals exceed 250 mL, the detrusor muscle can be stimulated to contract with bethanechol (Urecholine). Occasionally an indwelling Foley catheter may need to be placed for a few days.
- **Dysuria:** Pain with urination may be seen from urethral irritation from frequent intrapartum catheterizations. **Conservative management** may be all that is necessary. A urinary analgesic may be required occasionally.

Gastrointestinal Tract Changes

- **Constipation:** Decreased GI tract motility because of perineal pain and fluid mobilization, can lead to constipation. Management is oral hydration and stool softeners.
- **Hemorrhoids:** Prolonged second-stage pushing efforts can exaggerate preexisting hemorrhoids. **Management** is oral hydration and stool softeners.

OB Triad

Impaired Maternal–Infant Bonding

- Postpartum Day 1
- SVD: 1,900-g 31-week-old male in NICU
- Mom shows no interest in baby

OB Triad

Postpartum Blues

- Postpartum Day 2
- S/P SVD of term normal baby
- Mom cares for baby: tears

OB Triad

Postpartum Depression

- Postpartum Day 21
- S/P SVD of term normal baby
- Mom does not get out of bed, does not care for self or baby

OB Triad

Postpartum Psychosis

- Postpartum Day 21
- S/P SVD of term normal baby
- Mom exhibits bizarre behavior, hallucinations

Psychosocial Problems

High-Yield

- **Bonding:** Impaired maternal–infant bonding is seen in the first few days postdelivery. Lack of interest or emotions for the newborn is noted. Risk is increased if contact with the baby is limited because of neonatal intensive care, as well as poor social support. **Management** is psychosocial evaluation and support.
- **Blues:** Postpartum blues are very common within the first few weeks of delivery. Mood swings and tearfulness occur. Normal physical activity continues and care of self and baby is seen. **Management** is conservative with social support.
- **Depression:** Postpartum depression is common but is frequently delayed up to a month after delivery. Feelings of despair and hopelessness occur. The patient often does not get out of bed with care of self and baby neglected. **Management** includes psychotherapy and antidepressants.
- **Psychosis:** Postpartum psychosis is rare, developing within the first few weeks after delivery. Loss of reality and hallucinations occur. Behavior may be bizarre. **Management** requires hospitalization, antipsychotic medication, and psychotherapy.

Table I-18-1. Postpartum Psychosocial Problems

	Incidence	Symptoms	Where Treated	Management
Blues	**Common** 50–85%	Mood swings Tearfulness	Outpatient	Conservative Social support
Depression	**Common** 10–20%	Despair Hopelessness	Outpatient	Psychotherapy Antidepressants
Psychosis	**Rare** 0.01%	Loss of reality Hallucinations	Inpatient	Psychotherapy Antipsychotics

POSTPARTUM CONTRACEPTION AND IMMUNIZATIONS

Contraception Planning

- **Breast feeding:** Lactation is associated with temporary anovulation, so contraceptive use may be deferred for three months. A definitive method should be used after that time.
- **Diaphragm:** Fitting for a vaginal diaphragm should be performed after involution of pregnancy changes, usually at the six-week postpartum visit.
- **Intrauterine Device (IUD):** Higher IUD retention rates and decreased expulsions are seen if IUD placement takes place at six weeks postpartum.
- **Combination Modalities:** Combined estrogen-progestin formulations (e.g., pills, patch, vaginal ring) should not be used in breast-feeding women because of the estrogen effect of diminishing milk production. In nonlactating women, they should be started after three weeks postpartum to allow reversal of the hypercoagulable state of pregnancy and thus decrease the risk of deep venous thrombosis.
- **Progestin-only Contraception:** Progestin steroids (e.g., mini-pill, Depo-Provera, Nexplanon) do not diminish milk production so can safely be used during lactation. They can begin immediately after delivery.

Postpartum Immunizations

- **RhoGAM:** If the mother is Rh(D)-negative and her baby is Rh(D)-positive, she should be administered 300 μg of RhoGAM IM within 72 hours of delivery.
- **Rubella:** If the mother is rubella IgG antibody-negative, she should be administered active immunization with the live-attenuated rubella virus. She should avoid pregnancy for one month to avoid potential fetal infection.

POSTPARTUM HEMORRHAGE

Postpartum hemorrhage is vaginal delivery blood loss ≥500 mL **or** cesarean section blood loss ≥1,000 mL

Uterine Atony

High-Yield

Uterine atony is the **most common** cause (80%) of excessive postpartum bleeding.

Risk Factors. Rapid or protracted labor (**most common**), chorioamnionitis, medications (e.g., $MgSO_4$, β-adrenergic agonists, halothane), and overdistended uterus.

Clinical Findings. A soft uterus (feels like dough) palpable above the umbilicus.

Management. Uterine massage and uterotonic agents (e.g., oxytocin, methylergonovine, or carboprost).

Lacerations

High-Yield

Lacerations cause 15% of excessive postpartum bleeding.

Risk Factors. Uncontrolled vaginal delivery (**most common**), difficult delivery, and operative vaginal delivery.

Clinical Findings. Identifiable lacerations (cervix, vagina, perineum) in the presence of a contracted uterus.

Management. Surgical repair.

Retained Placenta

High-Yield

Retained placenta causes 5% of excessive postpartum bleeding.

Risk Factors. Accessory placental lobe (**most common**) and abnormal trophoblastic uterine invasion (e.g., cervix, vagina, perineum).

Clinical Findings. Missing placental cotyledons in the presence of a contracted uterus.

Management. Manual removal or uterine curettage under ultrasound guidance.

Disseminated Intravascular Coagulation

High-Yield

Disseminated intravascular coagulation (DIC) is rare.

Risk Factors. Abruptio placentae (**most common**), severe preeclampsia, amniotic fluid embolism, and prolonged retention of a dead fetus.

Clinical Findings. Generalized oozing or bleeding from IV sites or lacerations in the presence of a contracted uterus.

Management. Removal of pregnancy tissues from the uterus, intensive care unit (ICU) support, and selective blood-product replacement.

Uterine Inversion

High-Yield

Uterine inversion is rare.

Risk Factors. Myometrial weakness (most common) and previous uterine inversion.

Clinical Findings. Beefy-appearing bleeding mass in the vagina and failure to palpate the uterus abdominally.

Management. Uterine replacement by elevating the vaginal fornices and lifting the uterus back into its normal anatomic position, followed by IV oxytocin.

Table I-18-2. Postpartum Hemorrhage

Clinical	Diagnosis	Management
Uterus not palpable	**Inversion (rare)**	Elevate vaginal fornices, IV oxytocin
Uterus like dough	**Atony (80%)**	Uterine massage, oxytocin, ergot, PG F2α
Tears vagina, cervix	**Lacerations (15%)**	Suture & repair
Placenta incomplete	**Retain placenta (5%)**	Manual removal or uterine curettage
Diffuse oozing	**DIC (rare)**	Remove POC, ICU care, blood products prn
Persistent bleeding	**Unexplained (rare)**	Ligate vessels or hysterectomy

Unexplained

High-Yield

If despite careful searching no correctible cause of continuing hemorrhage is found, it may be necessary to perform a laparotomy and bilaterally surgically ligate the uterine or internal iliac arteries. Hysterectomy would be a last resort.

POSTPARTUM FEVER

Postpartum fever is defined as fever ≥38 C (≥100.4 F) on ≥2 occasions ≥6 hours apart, excluding first 24 hours postpartum.

PP Day 0: Atelectasis

High-Yield

Risk Factors. General anesthesia with incisional pain (**most common**) and cigarette smoking.

Clinical Findings. Mild fever with mild rales on auscultation. Patient is unable to take deep breaths.

Management. Pulmonary exercises (e.g., deep breaths, incentive spirometry) and ambulation. Chest x-rays are unnecessary.

PP Day 1–2: Urinary Tract Infection

High-Yield

Risk Factors. Multiple intrapartum catheterizations and vaginal examinations due to prolonged labor.

Clinical Findings. High fever, costovertebral flank tenderness, positive urinalysis (e.g., WBC, bacteria) and urine culture.

Management. Single-agent intravenous antibiotics.

PP Day 2–3: Endometritis

High-Yield

Endometritis is the **most common cause** of postpartum fever.

Risk Factors. Emergency cesarean section after prolonged membrane rupture and prolonged labor.

Clinical Findings. Moderate-to-high fever with exquisite uterine tenderness. Peritoneal signs should be absent and peristalsis should be present.

Management. Multiple-agent intravenous antibiotics (e.g., gentamycin and clindamycin) to cover polymicrobial genital tract flora.

PP Day 4–5: Wound Infection

High-Yield

Risk Factors. Emergency cesarean section after prolonged membrane rupture and prolonged labor.

Clinical Findings. Persistent spiking fever despite antibiotics, along with wound erythema, fluctuance, or drainage.

Management. Intravenous antibiotics for cellulitis. Wound drainage with twice-daily, wet-to-dry wound packing used for an abscess, anticipating closure by secondary intention.

PP Day 5–6: Septic Thrombophlebitis

High-Yield

Risk Factors. Emergency cesarean section after prolonged membrane rupture and prolonged labor.

Clinical Findings. Persistent wide fever swings despite broad-spectrum antibiotics with normal pelvic and physical examination.

Management. Intravenous heparin for 7–10 days, keeping PTT values at 1.5 to 2.0 times baseline.

PP Day 7–21: Infectious Mastitis

High-Yield

Risk Factors. Lactational nipple trauma leading to nipple cracking and allowing *Staphylococcus aureus* bacteria to enter breast ducts and lobes.

Clinical Findings. Fever of variable degree with localized, unilateral breast tenderness, erythema, and edema.

Management. Oral cloxacillin. Breast feeding can be continued. Ultrasound imaging is needed to rule out an abscess if lactational mastitis does not respond to antibiotics.

Table I-18-3. Postpartum Fever

Physical Exam	Diagnosis	Management
Lung "crackles" PP Day 0	**Atelectasis**	Ambulation, pulmonary exercises
Flank pain, dysuria PP Day 1–2	**Pyelonephritis**	Single IV antibiotic
Tender uterus PP Day 2–3	**Endometritis**	IV gentamicin and clindamycin
Wound purulence PP Day 5–6	**Wound infection**	Wet-to-dry packs
Pelvic mass PP Day 5–6	**Pelvic abscess**	Percutaneous drainage
"Picket fence" fever PP Day 5–6	**Septic thrombophlebitis**	Full heparinization

PART II

Gynecology

Basic Principles of Gynecology 1

Learning Objectives

- ❏ Provide an overview of female reproductive anatomy
- ❏ List the Tanner stages of development including expected changes and age of onset
- ❏ Describe the most common gynecologic procedures

FEMALE REPRODUCTIVE ANATOMY

Uterus

The **embryologic origin** of the uterus is from fusion of the two Müllerian ducts. **Major structures** include the corpus, cornu, isthmus and cervix. **Internal layers** of the uterus include the serosa, myometrium, and endometrium. The **ligaments** attached to the uterus include the broad ligament, round ligaments, cardinal ligaments, and uterosacral ligaments. **Anatomical positions** of the uterus include anteverted, retroverted, mid-position. Normal uterine position tips slightly anterior in the pelvis.

Oviducts

The oviducts **extend** from the uterus to the ovaries. **Segments** of the oviducts are the interstitium, isthmus, ampulla, and infundibulum. The oviducts function in facilitating sperm migration from the uterus to the ampulla and the transportation of the zygote toward the uterus. They are **attached** medially to the uterine corpus, laterally to the pelvic side wall, and inferiorly to the broad ligament. They receive dual **blood supply** from the ascending uterine artery and ovarian artery.

Ovaries

Functions of the ovaries include **containment** of oocytes within the ovarian follicles and **production** of reproductive and sexual hormones. The ovaries are **attached** by the ovarian ligament to the uterine fundus by the suspensory ligaments to the pelvic side wall, and by the mesovarium to the broad ligament. **Lymphatic drainage** of the ovaries is through the pelvic and paraaortic lymph nodes.

Vagina

The vagina is a tubular structure 8–9 cm in length that extends from the introitus to the cervix. The vagina traverses the urogenital diaphragm through the genital hiatus of the levator ani. It functions as the female copulatory organ, an outflow tract for menstrual flow, and birth canal in parturition.

GYNECOLOGIC PROCEDURES

Gynecologic Ultrasound

This imaging modality uses low-energy, high-frequency sound waves.

- **Transvaginal** transducers are utilized for lower pelvic masses, producing high-resolution images that are not influenced by the thickness of the maternal abdominal wall.
- **Transabdominal** transducers provide images throughout the entire pelvis as well as abdomen.
- Ultrasound works best when adjacent tissues have differing echodensities, particularly fluid/tissue interfaces.

Cervical Pap Smear

The cervical Pap smear, an outpatient office procedure, is a screening test for premalignant cervical changes that allows for early intervention and thus prevents cervical cancer. The diagnostic test for cervical dysplasia or cancer requires a histologic assessment made on a tissue biopsy specimen.

A Pap smear should include **cytologic specimens from two areas**: stratified squamous epithelium of transformation zone (TZ) of the ectocervix and columnar epithelium of the endocervical canal (EGG).

- **Ectocervix specimen:** Screening for squamous cell carcinoma, the most common cancer of the cervix (80%), involves scraping the TZ. The TZ is the area of the ectocervix between the old or "original" squamocolumnar junction (SCJ) and the new SCJ.
  - At puberty the vaginal pH falls, causing the "native" columnar epithelium to be transformed by metaplasia into normal-appearing "metaplastic" stratified squamous epithelium.
  - The TZ is the location where 95% of cervical dysplasia and cancer develop.
- **Endocervix specimen:** Screening for adenocarcinoma, the second most common cancer of the cervix (15%), involves scraping the endocervical canal with cytobrush.

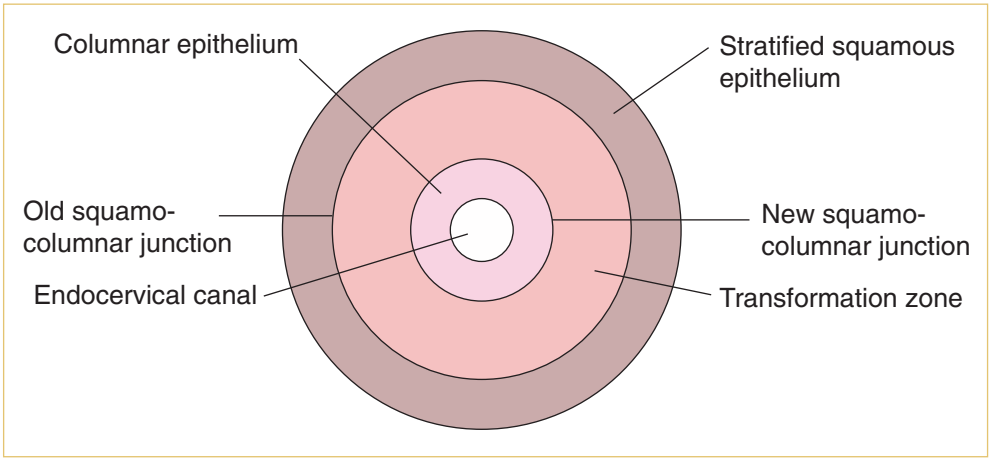


Figure II-1-1. Development of T-Zone

Studies show that while the "liquid-based" methods reduce the percentage of unsatisfactory specimens as compared with the "traditional" method, **both methods are equivalent in performance** for detection of cervical dysplasia.

- With **traditional Pap smear**, samples are obtained using a wooden **spatula** on the ectocervix and a **Cytobrush** for the endocervical canal rotating in one direction 360°. The cells from each area are then smeared evenly onto a glass slide, which is then fixed in formalin and then stained and examined under a microscope by a cytologist. **Potential problems** include insufficient smearing of all abnormal cells onto the glass slide, air drying artifacts if fixing is delayed, and clumping of cells, making cytology assessment difficult.
- With **liquid-based Pap smear**, specimens are obtained using a **cervical broom**. Long central bristles are placed into the endocervix and short outer bristles over the ectocervix. The broom is rotated 5 times in the same direction, collecting and sampling both endocervical cells and transformation zone. The cervical broom is placed in the preservative solution and rotated 10 times vigorously to release collected material into the solution. **Advantages** include a lower chance of abnormal cells being discarded with the collecting instrument, lower likelihood of air-drying artifacts, and more even spread of cells on the glass slide surface.

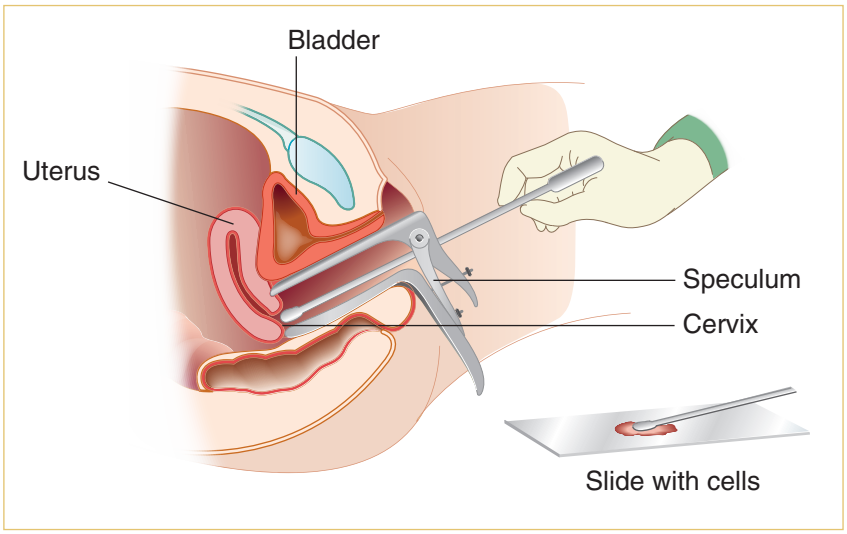


Figure II-1-2. Taking a Sample of Cells during Pap Smear

Colposcopy

Colposcopy is an outpatient office procedure. A binocular, short focal-length instrument with built-in light source is used to look at the cervix through a speculum. The purpose is to (1) visually identify where the abnormal Pap smear cells originated, and (2) biopsy that area to send for histologic diagnosis.

The ectocervix is visually examined to localize areas of abnormal epithelium. Dilute acetic acid is applied to the cervix to aid in the detection of dysplasia. Areas of abnormal-appearing tissue that are biopsied include **punctation**, **mosaicism**, **white epithelium**, and **abnormal vessels**. The specimens are sent to pathology for definitive diagnosis.

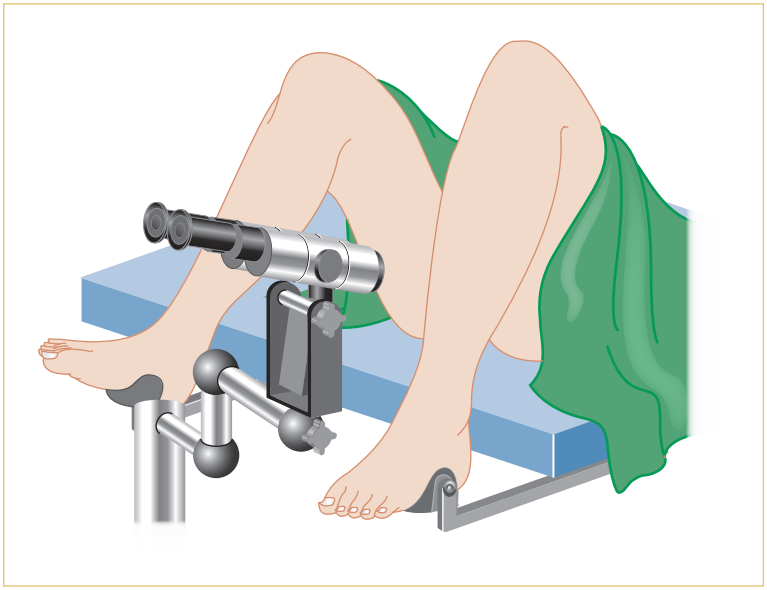


Figure II-1-3. Colposcopy

Endocervical Curettage

In endocervical curettage (ECC), the mucous membrane of the cervical canal is scraped at the time of colposcopy using a spoon-shaped instrument called a curette. This is usually is performed as a follow-up for an abnormal Pap smear.

- Performed if normal-appearing metaplastic epithelium is seen on colposcopy to enter the endocervical canal
- May also be performed if no lesion is identified on the ectocervix
- Not performed on pregnancy patients due to risk of heavy bleeding

Cold Knife Cone Biopsy

Cold knife cone biopsy is a minor outpatient surgical procedure performed in the operating room under local or general anesthesia. It is a diagnostic test that examines the histology of cervical lesions.

- A cone-shaped tissue specimen is obtained with a scalpel by performing a circumferential incision of the cervix with a diameter that is wider at the cervical os and narrower toward the endocervical canal. The tissue is sent to pathology for histologic diagnosis.
- **Wide-shallow cone** is performed if the Pap smear shows changes more severe than the colposcopically directed biopsy.
- **Narrow-deep cone** is performed if a lesion extends from the exocervix into the endocervical canal.
- Long-term risks include cervical **stenosis**, cervical **insufficiency**, and preterm birth.

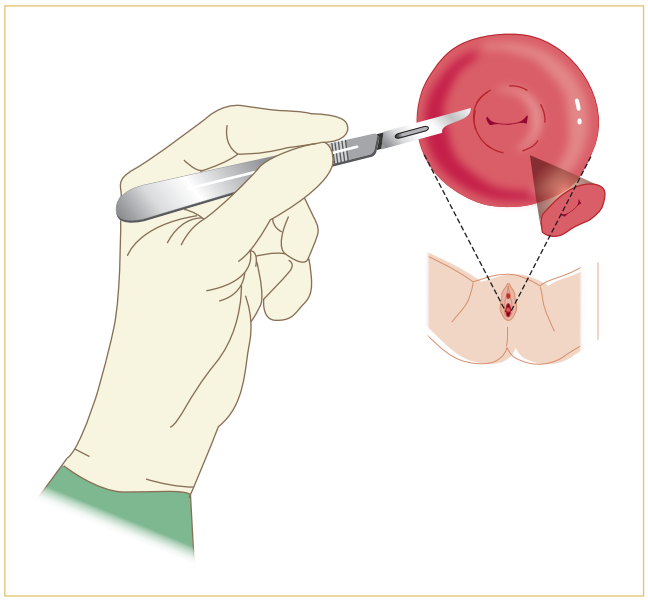


Figure II-1-4. Cold Knife Cone Biopsy

Loop Electrosurgical Excision Procedure

Loop electrosurgical excision procedure (LEEP) is a minor outpatient surgical procedure performed under local anesthesia. It is a diagnostic test that examines the histology of cervical lesions. Advantages are low cost, high success rate, and ease of use.

- This technique is used for diagnosing and treating cervical dysplasia. An electric current is passed through a thin wire loop to remove abnormal cervical tissues. The heated loop seals off blood vessels as it cuts.
- The tissue is sent to pathology. Follow-up Pap smears are performed every six months for two years to ensure that the dysplastic changes do not return.
- Long-term risks of LEEP include cervical stenosis and cervical insufficiency.

Cryotherapy

Cryotherapy is a minor outpatient procedure performed without anesthesia. It destroys dysplastic cervical tissue identified by colposcopy and cervical biopsy.

- A CryoProbe is placed over the abnormal cervical epithelium. The probe temperature is lowered to –50°C with liquid nitrogen. This causes the metal CryoProbe to freeze and destroy superficial abnormal cervical tissue. The freezing lasts for three minutes; the cervix is then allowed to thaw, and the freezing is repeated for another three minutes.
- A watery discharge will occur over the next few weeks as the destroyed tissue sloughs off. Follow-up Pap smears are performed every six months for two years to ensure that the dysplastic changes do not return.
- Long-term risks of cryotherapy include cervical **stenosis**.

Hysterectomy

Hysterectomy, removal of the uterus, is a major inpatient surgical procedure performed under either regional or general anesthesia. It is used for both diagnosis and therapy.

- Depending on the indications and pelvic exam, the procedure can be performed vaginally, abdominally, laparoscopically, or robot-assisted.
- **Subtotal** or supracervical hysterectomy removes only the corpus of the uterus, leaving the cervix in place.
- **Total hysterectomy**, the most common procedure, removes both the corpus and cervix of the uterus. Total hysterectomy is also known as **simple** hysterectomy.
- **Radical hysterectomy**, performed for early-stage cervical carcinoma, involves removal of the uterus, cervix, and surrounding tissues, including cardinal ligaments, uterosacral ligaments, and the upper vagina.

Hysteroscopy

Hysteroscopy is a minor outpatient surgical procedure performed in the operating room under either local-intravenous or general anesthesia for diagnosis and possibly for therapy.

- A fiberoptic scope is placed through a previously dilated cervix to directly visualize the endometrial cavity. A clear fluid is infused through side ports of the scope to distend the uterine cavity, allowing visualization.
- Other side ports of the hysteroscope can be used in placing instruments to biopsy lesions or to resect submucous leiomyomas, polyps, or uterine septa.

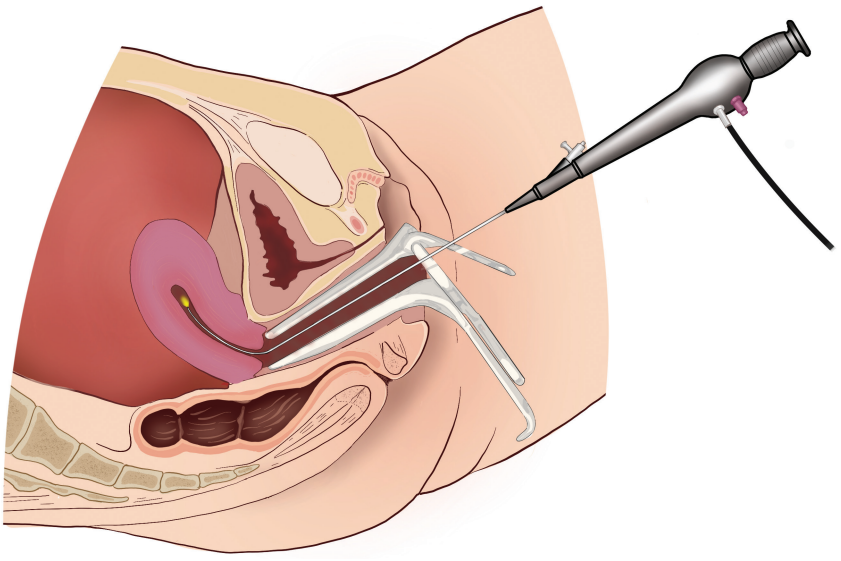


Figure II-1-5. Hysteroscopy

Laparoscopy

Laparoscopy is a minor outpatient surgical procedure performed in the operating room under general anesthesia for diagnosis and possibly for therapy.

- The abdominopelvic cavity is insufflated with pressured carbon dioxide to distend the abdomen and lift the abdominal wall away from the viscera. Through a port that is placed through the umbilicus, a fiberoptic scope is then inserted to visually examine the pelvis and abdomen.
- Common gynecologic indications for laparoscopy include diagnosing and treating causes of chronic pelvic pain (e.g., endometriosis or adhesions), resecting advanced ectopic pregnancies, and diagnosing and lysing tubal adhesions in infertility cases.

Hysterosalpingogram

Hysterosalpingogram (HSG) is a diagnostic outpatient radiologic imaging procedure performed without anesthesia. A cannula is placed in the endocervical canal and radio-opaque fluid is injected, allowing assessment of uterine malformations (e.g., uterine septum, bicornuate uterus) and Asherman's syndrome.

Tubal pathology can also be assessed by observing internal tubal anatomy and seeing whether the dye spills into the pelvic cavity.

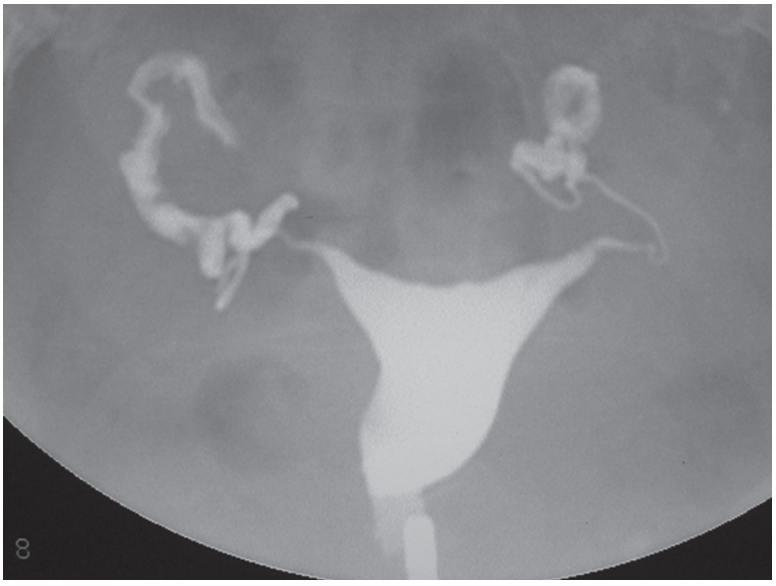


Figure II-1-6. Normal HSG

Dilation and Curettage

Dilation and curettage (D&C) is a minor outpatient surgical procedure performed under anesthesia in an operating room under either local-intravenous or general anesthesia. It is a diagnostic test that examines the histology of endometrial lesions.

D&C is performed similarly to an endometrial biopsy. However, the cervix frequently requires dilation with cervical dilators prior to introduction of the curette. The curette is used to scrape the endometrium, obtaining larger amounts of endometrial tissue that are then sent to pathology.

Endometrial Biopsy

Endometrial biopsy, an outpatient office procedure, is a diagnostic test that examines the histology of endometrial lesions.

The direction of the cervical canal and endometrial cavity is identified by placing a uterine sound through the endocervical canal. A hollow suction cannula is then placed into the uterine cavity and suction is applied. As the cannula is rotated, endometrial tissue is aspirated into it. When the cannula is removed, the retrieved tissue is placed in formalin and sent to pathology.

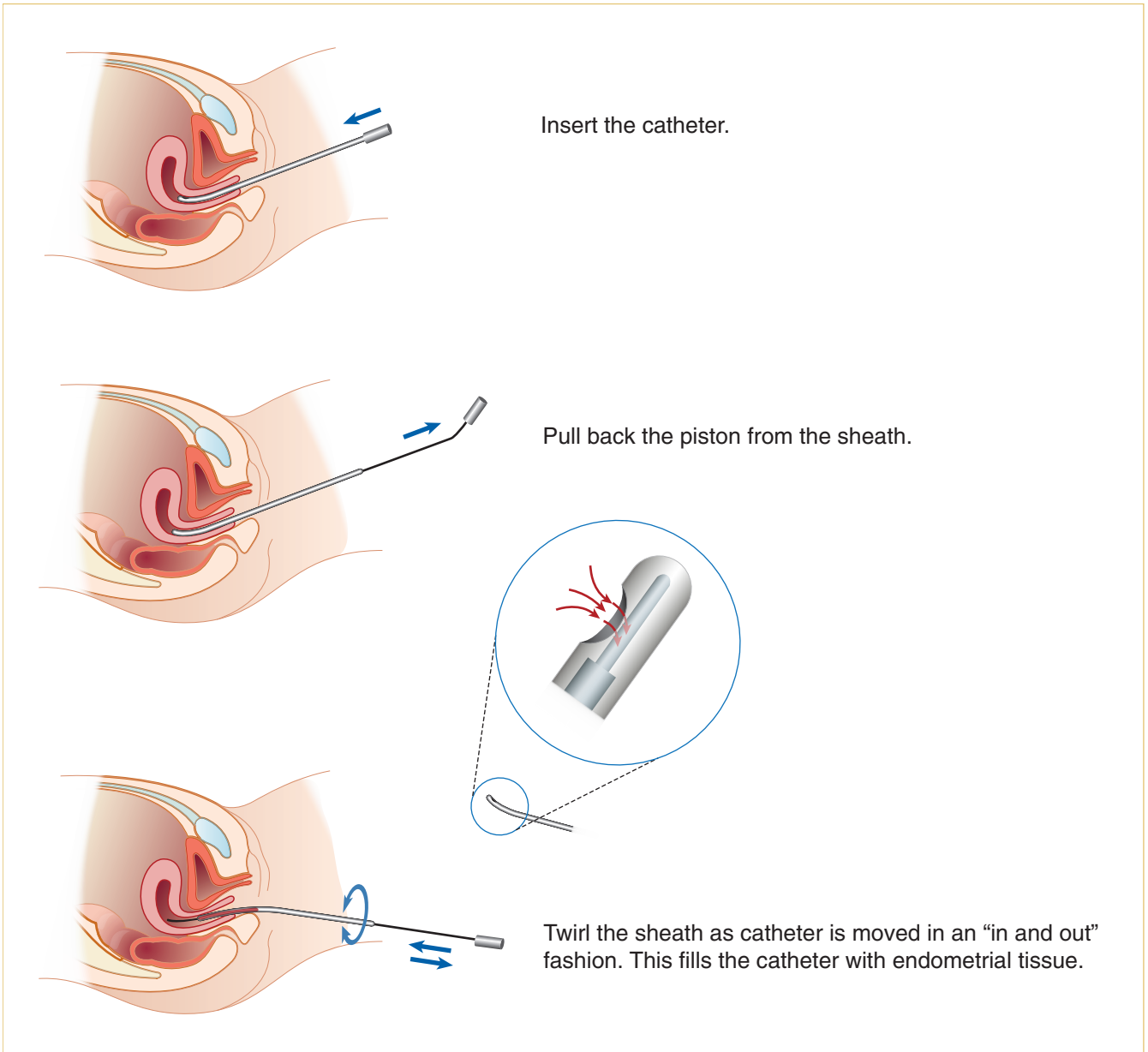


Figure II-1-7. Endometrial Biopsy

Vulvar Biopsy

Vulvar biopsy is a minor outpatient office procedure performed under local anesthesia. It is a diagnostic test that examines the histology of vulvar lesions that can be performed using a punch biopsy or a scalpel.

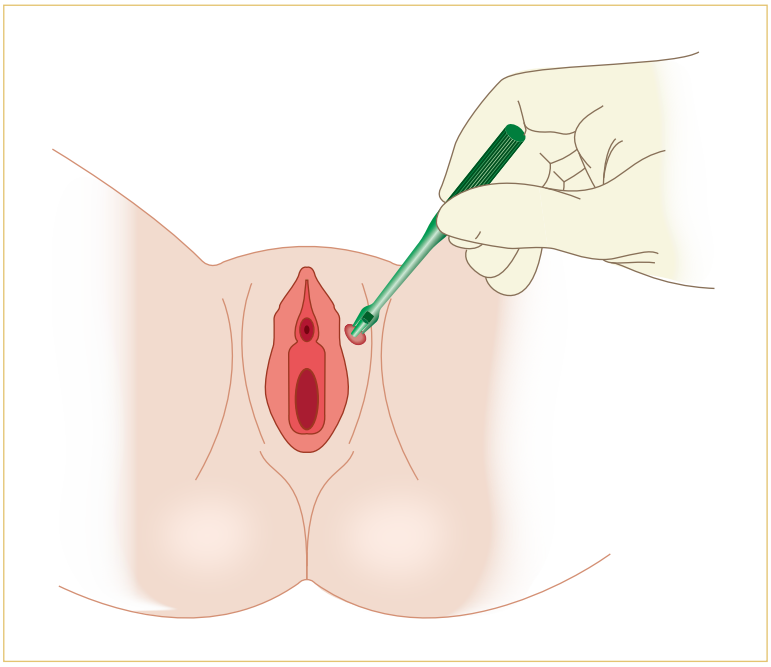


Figure II-1-8. Vulvar Biopsy

Pelvic Relaxation 2

Learning Objectives

- ❑ Demonstrate the relation between uterine/vaginal prolapse and urinary incontinence
- ❑ Describe other expected complications

PELVIC ORGAN PROLAPSE

A 62-year-old woman complains of low back pain and perineal pressure for 18 months. She had been recommended by another physician to wear a pessary, which she is reluctant to do. On pelvic examination a second-degree uterine prolapse with a cystocele and a rectocele is observed.

The pelvic floor is made up of the diaphragm and perineal membrane.

- The **pelvic diaphragm** consists of the levator ani and coccygeus muscles. The levator ani consists of three muscles: puborectalis, pubococcygeus, and iliococcygeus.
- The **perineal membrane** is a triangular sheet of dense fibromuscular tissue that spans the anterior half of the pelvic outlet. The vagina and the urethra pass through the perineal membrane (urogenital diaphragm).
- The main structures that **support the uterus** are the cardinal ligaments, the uterosacral ligaments, and the endopelvic fascia.

The etiology of pelvic relaxation is **most commonly related** to childbirth. The mechanical trauma of childbirth stresses and tears the supporting ligaments of the pelvic retroperitoneum in the pelvis, whose main function is to support the pelvic viscera. Advancing age and obesity are risk factors for pelvic organ prolapse (POP).

The components of pelvic relaxation include uterine prolapse, cystocele, rectocele, and enterocele. Lesser forms of pelvic relaxation include vaginal or vault prolapse.

The severity of prolapse is indicated by **increase in grade** from **1 to 4**:

- **Grade 1:** cervix descends halfway to the hymen
- **Grade 2:** cervix descends to the hymen
- **Grade 3:** cervix extends halfway past the hymen
- **Grade 4** (procidentia): entire uterus, as well as the anterior and posterior vaginal walls, extends outside the introitus

VAGINAL PROLAPSE

GYN Triad

Cystocele

- Postmenopausal woman
- Anterior vaginal wall protrusion
- Urinary incontinence

- **Cystocele:** herniation or bulging of the **anterior** vaginal wall and overlying bladder base into the vaginal lumen
- **Rectocele:** herniation or bulging of the **posterior** vaginal wall and underlying rectum into the vaginal lumen
- **Enterocele:** herniation of the **pouch of Douglas** containing small bowel into the vaginal lumen

The diagnosis of pelvic relaxation is mainly made through observation at the time of **pelvic examination**. The prolapsed vagina, rectum, and uterus are easily visualized, particularly as the patient increases intra-abdominal pressure by straining.

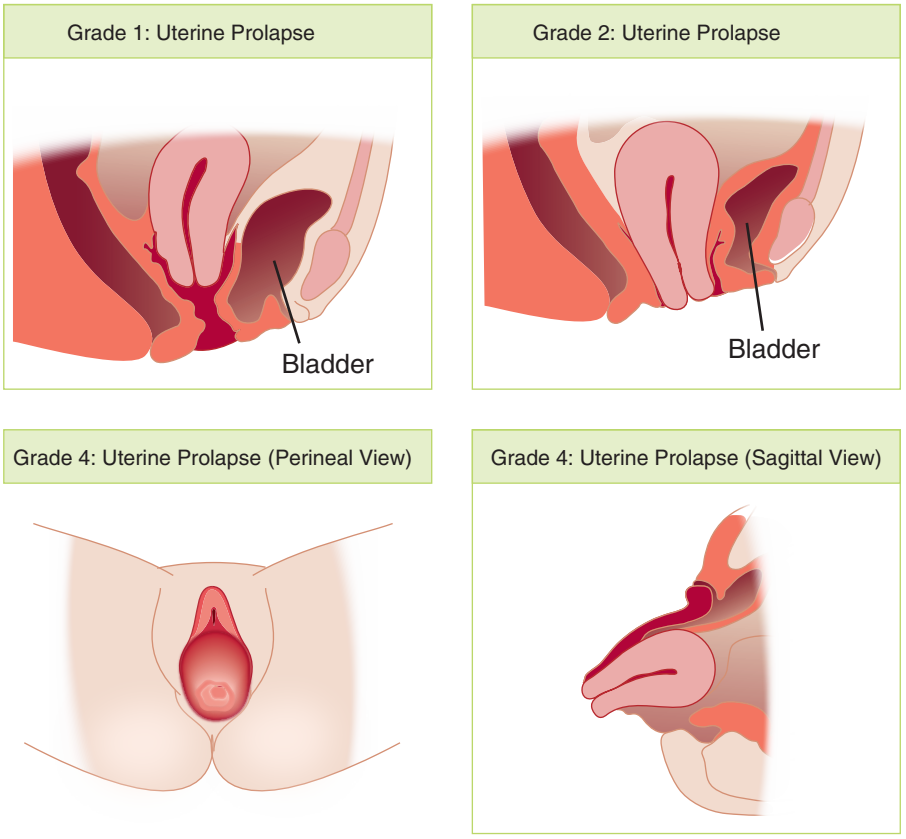


Figure II-2-1. Uterine Prolapse

GYN Triad

Rectocele

- Postmenopausal woman
- Posterior vaginal wall protrusion
- Digitally assisted removal of stool

Management. Non-surgical treatment for a minor degree of relaxation.

- **Kegel** exercises involve voluntary contractions of the pubococcygeus muscle.
- **Estrogen** replacement may be useful in postmenopausal women.
- **Pessaries** are objects inserted into the vagina that elevate the pelvic structures into their more normal anatomic relationships.

Surgical treatment when more conservative management has failed.

- The **vaginal hysterectomy** repairs the uterine prolapse, the anterior vaginal repair repairs the cystocele, and the posterior vaginal repair repairs the rectocele.
- The **anterior and posterior colporrhaphy** uses the endopelvic fascia that supports the bladder and the rectum, and a plication of this fascia restores normal anatomy to the bladder and to the rectum.

Limit strenuous activity for 3 months postoperatively to avoid recurrence of the relaxation.

URINARY INCONTINENCE

> A 58-year-old woman complains of urinary leakage after exertion. She loses urine while coughing, sneezing, and playing golf. She underwent menopause five years ago and is not on estrogen therapy. On examination there is evidence of urethral hypermobility with a positive Q-tip test.

Urinary incontinence is the inability to hold urine, producing involuntary urinary leakage.

The **physiology of continence** can be explained as follows:

- Continence and micturition involve a balance between urethral closure and detrusor muscle activity. Urethral pressure normally exceeds bladder pressure, causing urine to remain in the bladder.
- The proximal urethra and bladder are normally both within the pelvis.
- Intraabdominal pressure increases (from coughing and sneezing) are transmitted to both urethra and bladder equally, leaving the pressure differential unchanged, resulting in continence. Normal voiding is the result of changes in both of these pressure factors: urethral pressure falls and bladder pressure rises.
- Spontaneous bladder muscle (detrusor) contractions are normally easily suppressed voluntarily.

The **pharmacology of incontinence** can be explained as follows:

- **α-adrenergic receptors** are found primarily in the urethra and when stimulated cause contraction of urethral smooth muscle, preventing micturition. Drugs: ephedrine, imipramine, and estrogens. α-adrenergic blockers or antagonists relax the urethra, enhancing micturition. Drugs: phenoxybenzamine.
- **β-adrenergic receptors** are found primarily in the detrusor muscle and when stimulated cause relaxation of the bladder wall, preventing micturition. Drugs: flavoxate and progestins.
- **Cholinergic receptors** are found primarily in the detrusor muscle and when stimulated cause contraction of the bladder wall, enhancing micturition. Drugs: bethanechol and neostigmine. Anticholinergic medications block the receptors, inhibiting micturition. Drugs: oxybutynin and propantheline.

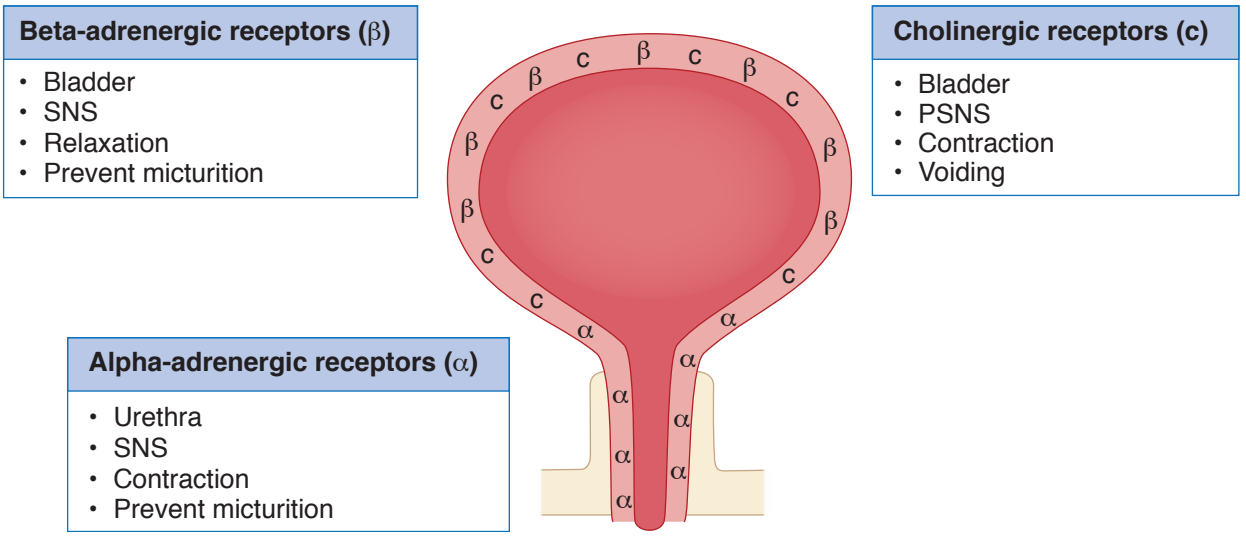


Figure II-2-2. Continence and Micturition

Evaluation of Incontinence

History. The patient should complete a 3-day (full, 24-hour days) voiding diary, a record of the bladder's behavior that helps to identify the diagnosis.

- List the amount of fluid taken in and the amount of urine produced.
- Record each individual drink with its volume, each voiding with its volume (by using a measuring cup), and each incident of urine loss.
- For each event, record how much urge is felt and whether there is pain at, before, or after voiding.
  - Urine loss with physical activity suggests **stress**.
  - Urge to empty but not getting to the toilet fast enough suggests **urge**.
  - Incontinence with both physical activity and sense of urgency suggests **mixed**.
  - Continuous loss of urine day and night suggests **fistula**.

Physical Exam. An **abdominal** exam should rule out masses, ascites, and organomegaly, which can influence intra-abdominal pressure.

- Assess **pudendal** nerve innervation of the perineum with the bulbocavernosus and clitoral sacral reflex (lightly brushing the labia majora or tapping the clitoris should produce a reflex of the external anal sphincter muscle).
- Do pelvic exam to evaluate for inflammation, infection, and atrophy, which can increase **bladder** sensitivity and lead to urgency, frequency, and dysuria.
- **Vaginal wall** prolapse findings will identify cystocele, rectocele, and enterocele.
- Perform **Q-tip test** to assess for hypermobility of the urethrovesical junction. With patient in supine position, place a sterile, well-lubricated cotton-tipped swab in the urethra (angle the swab **<30 degrees from the horizontal**; with inadequate bladder neck support, angle will be >30 degrees)

Urinalysis & Culture. A urinalysis should be performed in all patients, looking for leukocytes (WBC), bacteria, and RBC.

- Many **WBC** and **bacteria** would suggest a UTI; do urine culture for identification of bacteria and antibiotic sensitivities. Treat with appropriate antibiotics.
- Microscopic **hematuria** would suggest a bladder stone or foreign body and tumor. Do further work-up with cystoscopy.

Table II-2-1. Cystometric Volume Measurements

Post-void residual	<100 mL
Sensation of fullness	200–225 mL
Urge to void	400–500 mL

Cystometric Studies. Basic office cystometry begins with the patient emptying the bladder as much as possible. A urinary catheter is first used to empty the bladder and then left in place to infuse saline by gravity retrograde assessing the following:

- **Residual volume:** how much is left in bladder after voiding (normal <100 mL)
- **Sensation-of-fullness volume:** how much infusion (in mL) until patient senses fluid in bladder (normal 200–225 mL)
- **Urge-to-void volume:** how much infusion (in mL) until patient feels the need to empty bladder (normal 400–500 mL)
- **Involuntary bladder contractions:** detect involuntary detrusor contractions by watching saline level in syringe rise or fall (absence of contractions is normal)

Classification of Incontinence

Most of the following types of incontinence result when bladder pressure rises in isolation of increases in urethral pressure.

Genuine stress incontinence (most common incontinence in **young women**) is the result of rises in bladder pressure due to intra-abdominal pressure increases (e.g., coughing and sneezing). These rises in bladder pressure are not transmitted to the proximal urethra because it is no longer a pelvic structure, owing to loss of support from pelvic relaxation. This may be associated with urethral hypermobility (see Q-tip test) or less commonly with intrinsic sphincteric deficiency.

- **History.** Loss of urine occurs in small spurts simultaneously with coughing or sneezing. **It does not take place when the patient is asleep**.
- **Examination.** Pelvic examination may reveal a cystocele. Neurologic examination is normal. The Q-tip test is positive—when a lubricated cotton-tip applicator is placed in the urethra and the patient increases intraabdominal pressure, the Q-tip will rotate >30 degrees.
- **Investigative studies.** Urinalysis and culture are normal. Cystometric studies are normal with no involuntary detrusor contractions seen.
- **Management.** Medical therapy includes Kegel exercises and estrogen replacement in postmenopausal women. Surgical therapy aims to elevate the urethral sphincter so that it is again an intraabdominal location (urethropexy). This is done by attachment

GYN Triad

Stress Incontinence

- Involuntary loss of urine
- With coughing and sneezing
- No urine lost at night

of the sphincter to the symphysis pubis, using the Burch procedure as well as the Marshall-Marchetti-Krantz (MMK) procedure. The success rate of both of these procedures is 85–90%. A minimally invasive surgical procedure is the tension-free vaginal tape procedure in which a mesh tape is placed transcutaneously around and under the mid urethra. It does not elevate the urethra but forms a resistant platform against intra-abdominal pressure.

GYN Triad

Hypertonic Bladder

- Involuntary loss of urine
- Cannot suppress urge to void
- Urine loss day and night

Motor urge (hypertonic) incontinence (most common incontinence in **older women**) is the result of involuntary rises in bladder pressure, occurring from idiopathic detrusor contractions that cannot be voluntarily suppressed.

- **History.** Loss of urine occurs in large amounts often without warning. This can take place both day and night. The most common symptom is urgency.
- **Examination.** Pelvic examination shows normal anatomy. Neurologic examination is normal.
- **Investigative studies.** Urinalysis and culture are normal. Cystometric studies show normal residual volume, but involuntary detrusor contractions are present even with small volumes of urine in the bladder.
- **Management.** Anticholinergic medications (e.g., oxybutynin); NSAIDs to inhibit detrusor contractions; tricyclic antidepressants; calcium-channel blockers.

Mixed incontinence (mostly older women) is a combination of both stress and urge incontinence. The contribution of each type of involuntary urine loss varies by individual.

- **History.** Loss of urine may occur with **both** physical activity, coughing and sneezing as well as after experiencing an overwhelming urge to urinate.
- **Examination.** Pelvic exam may or may not show vaginal prolapse (cystocele, rectocele, or enterocele). Q-tip test is variable. Pudendal nerve innervation will be normal.
- **Investigative studies.** Urinalysis will be unremarkable. Cystometry will show a normal residual volume, but sensation-of-fullness and urge-to-void volume may be decreased. Involuntary detrusor contractions may be seen.
- **Management.** No single therapy works for everyone; options will be directed by whether the stress or the urge component is greater.

With **functional incontinence** (mostly older women), urinary storage and emptying functions are intact but the patient is unable to get to the toilet on time, whether physically challenged (not moving quickly enough out of a wheelchair due to arthritis or Parkinson's disease) or psychologically challenged (unclear thinking or communication due to Alzheimer's or dementia).

- **History.** Primary finding is inability to toilet oneself in a timely fashion. Loss of urine can vary, from small leakages to full emptying of the bladder.
- **Examination.** Varies with individual but the bladder support and innervation are intact.
- **Investigative studies.** Urinalysis and cystometry will be unremarkable. Involuntary detrusor contractions are not seen.
- **Management.** Treatment of the underlying medical condition; possible bladder training and pelvic floor exercises (Kegel exercises).

With **overflow (hypotonic) incontinence**, a rise in bladder pressure occurs gradually from an overdistended, hypotonic bladder. When the bladder pressure exceeds the urethral pressure, involuntary urine loss occurs but only until the bladder pressure equals urethral pressure. **The bladder never empties**. Then the process begins all over. This may be caused by denervated bladder (e.g., diabetic neuropathy, multiple sclerosis) or systemic medications (e.g., ganglionic blockers, anticholinergics).

- **History.** Loss of urine occurs intermittently in small amounts. This can take place **both day and night**. The patient may complain of pelvic fullness.
- **Examination.** Pelvic examination may show normal anatomy; however, the neurologic examination will show decreased pudendal nerve sensation.
- **Investigative studies.** Urinalysis and culture are usually normal, but may show an infection. Cystometric studies show **markedly increased residual volume**, but involuntary detrusor contractions do not occur.
- **Management.** Possible intermittent self-catheterization, discontinuation of the offending systemic medications, cholinergic medications to stimulate bladder contractions, and α-adrenergic blocker to relax the bladder neck.

GYN Triad

Hypotonic Bladder

- Involuntary loss of urine
- Detrusor muscle not contracted
- Urine loss day and night

With **fistula**, the normal urethral-bladder mechanism is intact but is bypassed by urine leaking out through a fistula from the urinary tract.

- **History.** The patient usually has a history of radical pelvic surgery or pelvic radiation therapy. Loss of urine **occurs continually** in small amounts. This can take place **both day and night**.
- **Examination.** Pelvic examination may show normal anatomy and normal neurologic findings.
- **Investigative studies.** Urinalysis and culture are normal. An intravenous pyelogram (IVP) will demonstrate dye leakage from a urinary tract fistula. With a urinary tract-vaginal fistula, intravenous indigo carmine dye will leak onto a vaginal tampon.
- **Management.** Surgical repair of the fistula.

GYN Triad

Bypass Incontinence

- Involuntary loss of urine
- History: radical pelvic surgery or radiation
- Urine loss day and night continuously

Disorders of the Vagina and Vulva

3

Learning Objectives

- ❑ Describe the common causes, diagnosis, and treatment of vaginal discharge
- ❑ List the most common vulvar diseases

VAGINAL DISCHARGE

A 25-year-old woman complains of a whitish vaginal discharge. She states that this is the first time she has this complaint, and it is associated with vaginal and vulvar pruritus. There is no significant medical history, and she is not on oral contraception.

Diagnostic Tests.

- **Visual inspection:** The vulva and vagina should be examined for evidence of an inflammatory response as well as the gross characteristics of the vaginal discharge seen on speculum examination.
- **Vaginal pH:** Normal vaginal pH is an acidic <4.5. Identification of the pH is easily performed using pH-dependent Nitrazine paper. Normal vaginal discharge leaves the paper yellow, whereas an elevated pH turns the paper dark.
- **Microscopic examination:** Two drops of the vaginal discharge are placed on a glass slide with a drop of normal saline placed on one, and a drop of KOH placed on the other. The two sites are covered with cover slips and examined under the microscope for WBC, pseudohyphae, trichomonads, and clue cells.

Bacterial Vaginosis

Bacterial vaginosis is the **most common** (50%) cause of vaginal complaints in the United States. It is not a true infection, but rather an alteration in concentrations of normal vaginal bacteria. The normal predominant lactobacilli are replaced by massive increases in concentrations of anaerobic species and facultative aerobes. It is frequently seen postmenopausally because of low levels of estrogen.

Bacterial vaginosis is not sexually transmitted, but rather is associated with sexual activity. The **most common** patient complaint is a fishy odor. Itching and burning are not present.

Speculum Examination. The vaginal discharge is typically thin, grayish-white. No vaginal inflammation is noted. Vaginal pH is elevated >4.5. A positive **"whiff"** test is elicited when KOH is placed on the discharge, releasing a fishy odor.

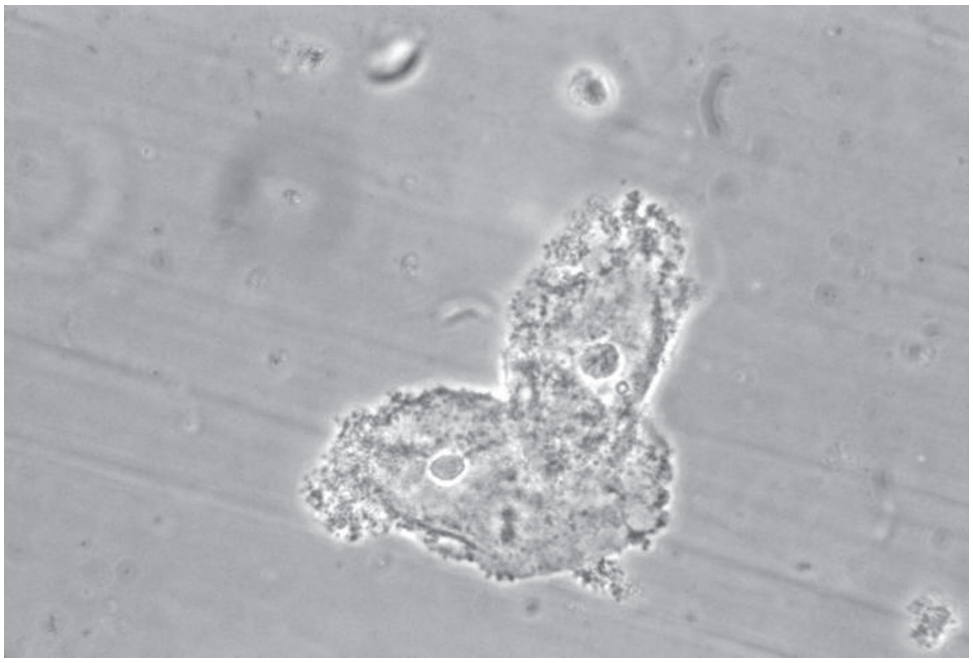
Wet Mount. Microscopic examination reveals **"clue cells"** on a saline preparation. These are normal vaginal epithelial cells with the normally sharp cell borders obscured by increased numbers of anaerobic bacteria. WBCs are rarely seen.

Management. Oral or vaginal metronidazole or clindamycin; metronidazole is safe during pregnancy (including first trimester).

GYN Triad

Bacterial Vaginosis

- Vaginal discharge pH >4.5
- Fishy odor
- "Clue" cells



phil.cdc.gov

Figure II-3-1. Clue Cells on Wet Mount

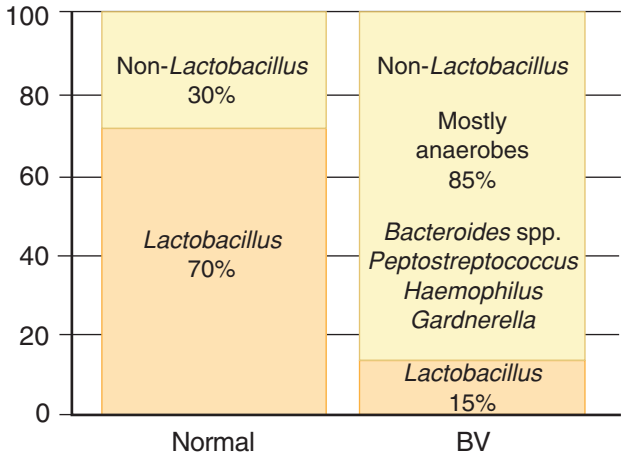


Figure II-3-2. Change in Vaginal Flora with Bacterial Vaginosis (BV)

GYN Triad

Trichomonas Vaginitis

- Vaginal discharge >4.5
- Itching and burning
- "Strawberry" cervix

Trichomonas Vaginitis

Trichomonas vaginitis is the **most common cause of vaginal complaints worldwide** and the second most common sexually transmitted disease **(STD)** in the United States. It is caused by a flagellated pear-shaped protozoan that can reside asymptomatically in male seminal fluid.

The **most common patient complaint** is vaginal discharge associated with itching, burning, and pain with intercourse.

Speculum Examination. Vaginal discharge is typically frothy and green. The vaginal epithelium is frequently edematous and inflamed. The erythematous cervix may demonstrate the characteristic **"strawberry"** appearance. Vaginal pH is elevated >4.5.

Wet Mount. Microscopic examination reveals actively motile "trichomonads" on a saline preparation. WBCs are seen.

Management. Oral metronidazole for both the patient and her sexual partner. Vaginal metronidazole gel has a 50% failure rate. Metronidazole is safe during pregnancy (including first trimester).

Candida (Yeast) Vaginitis

Candida (yeast) vaginitis is the **second most common vaginal complaint in the United States**. The **most common** organism is *Candida albicans*. It is not transmitted sexually.

Risk factors include diabetes mellitus, systemic antibiotics, pregnancy, obesity, and decreased immunity.

The **most common patient complaint** is itching, burning, and pain with intercourse. *Candida* vaginitis is seen in non-sexually active patients as well.

Speculum Examination. Vaginal discharge is typically curdy and white. The vaginal epithelium is frequently edematous and inflamed. Vaginal pH is normal <4.5.

Wet Mount. Microscopic examination reveals **pseudohyphae** on a KOH prep. WBCs are frequently seen.

Management. Either a single oral dose of fluconazole or a vaginal "azole" cream. An asymptomatic sexual partner does not need to be treated.

Speculum Exam:
Saline prep
KOH prep

Fishy odor
pH >4.5

Bacterial Vaginosis
#1 in US: anaerobes>lactobacillus
Discharge: thin, gray, **+ whiff test**
Wet Mount: no WBC, yeast but + "clue" cells
Rx: **Metronidazole** or **clindamycin** (not STD)

Itching Burning
pH >4.5

Trichomonas Vaginitis
#1 in world protozoa, **STD**
Discharge: frothy & green, "strawberry cervix"
Wet Mount: WBC & motile trichomonads (saline)
Rx: **Metronidazole** (treat sex partner)

Itching Burning
pH <4.5

Yeast Vaginitis
#2 in US: Candida species common, not STD
Discharge: "cottage cheese"
Wet Mount: WBC (saline) hyphae (KOH)
Rx: PO **fluconazole** or "**azole**" creams (not STD)

Used with permission: Elmar Sakala, MD

Figure II-3-3. Vaginal Discharge

GYN Triad

Candida (Yeast) Vaginitis

- Vaginal discharge pH <4.5
- Itching and burning
- Pseudohyphae

Physiologic Discharge

Physiologic discharge is the result of the thin, watery cervical mucus discharge seen with estrogen dominance. It is a normal phenomenon and becomes a complaint with prolonged anovulation, particularly in patients with wide eversion of columnar epithelium.

Risk factors include chronic anovulatory conditions such as polycystic ovarian syndrome (PCOS).

The **most common patient complaint** is increased watery vaginal discharge. There is no burning or itching.

Speculum Exam. The columnar epithelium of the endocervical canal extends over a wide area of the ectocervix, producing abundant mucus discharge. Vaginal discharge is typically thin and watery. The vaginal epithelium is normal, appearing with no inflammation. Vaginal pH is normal (<4.5).

Wet Mount. Microscopic examination reveals an absence of WBCs, "clue cells," trichomonads, or pseudohyphae.

Management. Steroid contraception with progestins, which will convert the thin, watery, estrogen-dominant cervical discharge to a thick, sticky progestin-dominant mucus.

VULVAR DISEASES

Benign Vulvar Lesions

- **Molluscum contagiosum.** A common benign, viral skin infection. Most commonly seen in children, sexually active adults, and immunodeficient patients. The molluscipox virus causes spontaneously regressing, umbilicated tumors of the skin rather than pox-like vesicular lesions. Molluscum contagiosum is transmitted primarily through direct skin contact with an infected individual. **Management** includes observation, curettage, and cryotherapy.
- **Condylomata acuminata.** These are benign cauliflower-like vulvar lesions due to HPV types 6 & 11. They have no malignant predisposition. Condylomata are discussed in detail in chapter 7. **Management** is treatment of the clinical lesions only.
- **Bartholin cyst.** If the orifice of the Bartholin duct becomes obstructed, mucous produced by the gland accumulates, leading to cystic dilation proximal to the obstruction. Obstruction is often caused by local or diffuse vulvar edema. Bartholin cysts are usually sterile. **Management** is conservative unless pressure symptoms occur due to size.
- **Bartholin abscess.** An abscess of the Bartholin gland may occur due to infection (mostly caused by *E. coli* and anaerobic *Bacteroides* species, and seldom due to gonococcus). **Management.** Outpatient treatment is I&D with placement of a Word catheter under local anesthesia. The balloon is inflated and left in place for a month to allow a drainage tract to form. Antibiotic treatment is usually not needed.

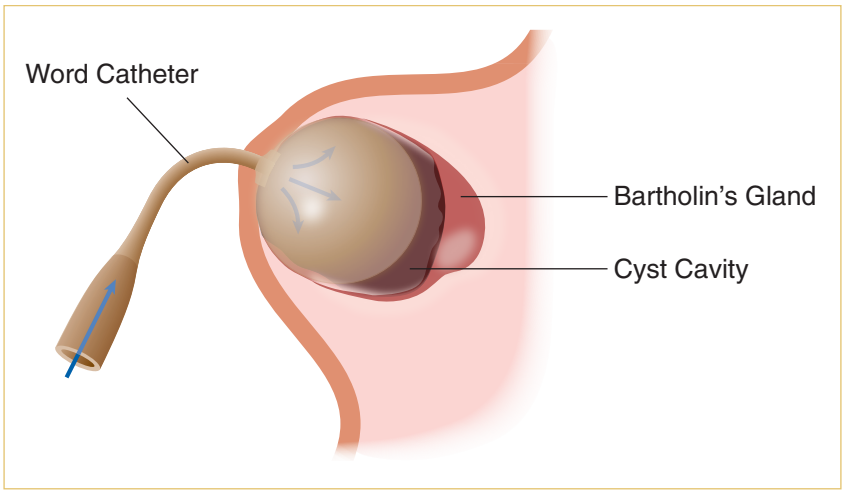


Figure II-3-4. Use of Word Catheter

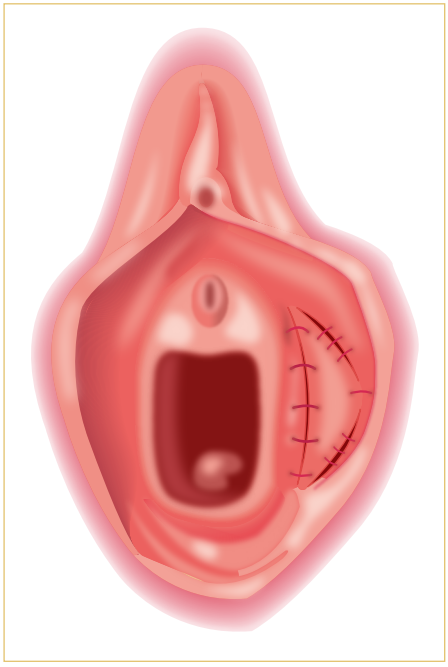


Figure II-3-5. Marsupialization

Vulvar Lesion with Pruritus/Neoplasia

A 70-year-old woman complains of vulvar itching for a year. She has been treated with multiple steroid medications with no relief. On pelvic examination there is a well-defined, 1 cm white lesion of the left labia minora. No other lesions in the vulva are noted; however, there is a clinical enlargement of a left inguinal node.

The **most common symptom** of both benign and malignant lesions is **vulvar itching**, resulting in scratching. Differential diagnosis includes sexually transmitted diseases, benign vulvar dermatosis, or cancers.

Premalignant vulvar dermatosis

These are benign lesions with **malignant predisposition**. The most common symptom is vulvar itching, but most lesions are asymptomatic.

Note

Vulvar dystrophies must also be considered in patients presenting with vulvar itching.

- **Squamous hyperplasia.** These lesions appear as whitish focal or diffuse areas that are firm and cartilaginous on palpation. Histologically, they show thickened keratin and epithelial proliferation. **Management** is fluorinated corticosteroid cream.
- **Lichen sclerosus.** This appears as bluish-white papula that can coalesce into white plaques. On palpation they feel thin and parchment-like. Histologically, they show epithelial thinning. **Management** is clobetasol cream.
- **Squamous dysplasia.** These lesions appear as white, red, or pigmented and are often multifocal in location. Histologically, they show cellular atypia restricted to the epithelium without breaking through the basement membrane. The appearance is almost identical to cervical dysplasia. **Management** is surgical excision.
- **CIS.** The appearance is indistinguishable from vulvar dysplasia. Histologically, the cellular atypia is full thickness but does not penetrate the basement membrane. **Management** is laser vaporization and vulvar wide local excision.

Malignant vulvar lesions

Vulvar carcinoma is an **uncommon** gynecologic malignancy, with mean age at diagnosis age 65. It is the fourth most common gynecologic malignancy. Risk factors include older age, cigarette smoking, HIV, and premalignant vulvar dermatosis.

- **Squamous cell** (90%). The **most common** type of invasive vulvar cancer is squamous cell carcinoma, which has been associated with HPV. Pathogenesis is chronic inflammation (for older women) and HPV infection (for younger women). The **most common** stage at diagnosis is stage 1.
- **Melanoma** (5%). The **second most common** histologic type of vulvar cancer is melanoma of the vulva, and the most important prognostic factor for this type of tumor is the depth of invasion. Any dark or black lesion in the vulva should be biopsied and considered for melanoma.
- **Paget's disease.** An uncommon histologic lesion is Paget's disease of the vulva. Paget's disease is characteristically a **red lesion**, which is **most common** in postmenopausal white women. Any patient with a red vulvar lesion must be considered for the possibility of Paget's disease. Most of the time Paget's disease is an intraepithelial process; however, in approximately 18–20% of cases invasion of the basement membrane has been identified. Patients with Paget's disease of the vulva have a higher association of other cancers mainly from the GI tract, the genitourinary system, and breast.

There is **no screening** test.

Diagnosis. All vulvar lesions of uncertain etiology should be **biopsied**. Patients with vulvar pruritus should be considered for the possibility of preinvasive or invasive vulvar carcinomas if there is a vulvar lesion. A biopsy of this patient's lesion reveals invasive squamous cell carcinoma of the vulva.

Pattern of spread starts with local growth and extension that embolizes to inguinal lymph nodes, and then sees hematogenous spread to distant sites.

Staging. Staging is **surgical** and utilizes the **TNM** (tumor, nodes, metastasis) classification. **Stage 1 is the most common stage**.

Management.

- **Wide local excision only:** used only for stage IA; risk of metastasis is negligible so no lymphadenectomy is needed
- **Modified radical vulvectomy:** involves radical local excision
  - Ipsilateral inguinal dissection is used only if stage is IB & unifocal, lesion >1 cm from midline, AND no palpable nodes
  - Bilateral inguinal dissection is used if at least stage IB or a centrally located lesion OR palpable inguinal nodes or positive ipsilateral nodes
- **Radical vulvectomy:** involves removal of labia minora & majora, clitoris, perineum, perineal body, mons pubis; seldom performed due to high morbidity
- **Pelvic exenteration.** In addition to radical vulvectomy, it involves removal of cervix, vagina, and ovaries in addition to lower colon, rectum, and bladder (with creation of appropriate stomas); seldom indicated or performed due to high morbidity.
- **Radiation therapy:** used for patients who cannot undergo surgery

Table II-3-1. Management of Vulvar Carcinoma

Radical vulvectomy	Removes entire vulva (subcutaneous and fatty tissue, labia minora and majora, perineal skin, clitoris)	Sexual dysfunction
Modified radical vulvectomy	Wide local excision (for **unilateral** labial lesions that do not cross the midline)	Less sexual morbidity
Lymphadenectomy	Inguinal node dissection (**bilateral** if midline lesions >1 mm invasion; **unilateral** selectively)	Lower-extremity edema

Disorders of the Cervix and Uterus

4

Learning Objectives

- ❑ Explain the use of vaccination to prevent cervical dysplasia
- ❑ List the common findings and their significance when diagnosing cervical lesions
- ❑ Give an overview of the epidemiology and management of cervical neoplasia
- ❑ Describe Müllerian anomalies
- ❑ Give a differential diagnosis for enlarged uterus and describe the treatment and prognosis of endometrial neoplasia

CERVICAL LESIONS

Cervical Polyps

Cervical polyps are finger-like growths that start on the surface of the cervix or endocervical canal. These small, fragile growths hang from a stalk and push through the cervical opening. Their cause is not completely understood; they may be associated with chronic inflammation, an abnormal response to increased levels of estrogen, or thrombosed cervical blood vessels.

Cervical polyps are relatively common, especially in older multiparous women. In most cases only a single polyp is present, but sometimes two or three are found.

- History is usually positive for vaginal bleeding, often after intercourse; this bleeding occurs between normal menstrual periods.
- Speculum examination reveals smooth, red or purple finger-like projections from cervical canal.
- Cervical biopsy typically reveals mildly atypical cells and signs of infection.

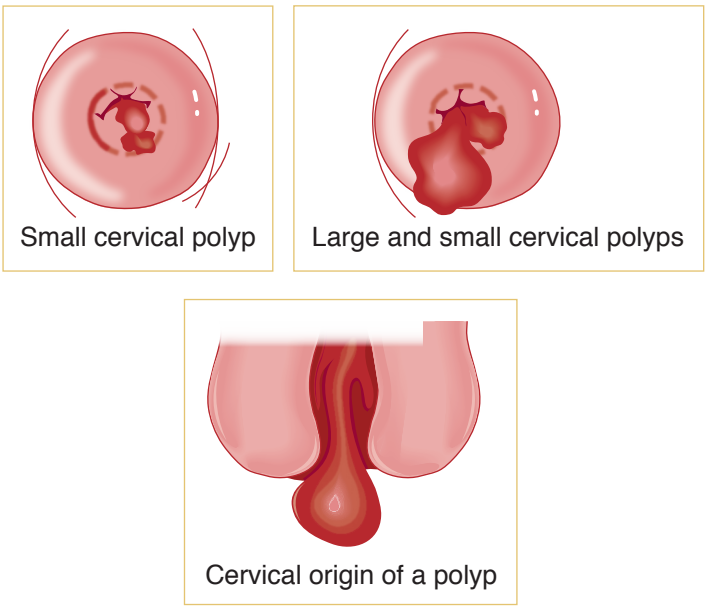


Figure II-4-1. Cervical Polyps

Management. Remove with gentle twisting or by tying a surgical string around the base and cutting it off (the base is removed by electrocautery or laser). Post-removal, give antibiotics even in the absence of infection because many polyps are infected. Although most cervical polyps are benign, the removed tissue should be sent to pathology. Regrowth of polyps is uncommon.

Nabothian Cysts

Nabothian cysts are mucus-filled cysts on the surface of the uterine cervix. The cervical canal is lined by glandular cells that normally secrete mucus. These endocervical glands can become covered by squamous epithelium through metaplasia.

This is a benign condition. Rarely, cysts may become so numerous or enlarged that the cervix becomes clinically enlarged.

- These nests of glandular cells (nabothian glands) on the cervix may become filled with secretions. As secretions accumulate, a smooth, rounded lump may form just under the surface of the cervix and become large enough to be seen or felt upon examination.
- Each cyst appears as a small, white, pimple-like elevation. The cysts can occur singly or in groups, and they are not a threat to health. The cysts are more common in women of reproductive age, especially women who have already had children. There are no observable symptoms.

Pelvic examination reveals a small, smooth, rounded lump (or collection of lumps) on the surface of the cervix. Rarely, a colposcopic exam is necessary to distinguish nabothian cysts from other types of cervical lesions.

Management. No treatment necessary; however, nabothian cysts do not clear spontaneously. They can be easily cured through electrocautery or cryotherapy, either of which can be done in the doctor's office.

Cervicitis

Often with cervicitis, there are no symptoms except vaginal discharge. The **most common findings** are mucopurulent cervical discharge and a friable cervix. This diagnostic finding is confirmed by endocervical bleeding easily induced by passage of a cotton swab through the cervical os. No pelvic tenderness is noted. Patient is afebrile.

Routine cervical cultures are positive for chlamydia or gonorrhea. WBC and ESR are normal.

Management. Oral azithromycin in a single dose or oral doxycycline BID for 7 days

CERVICAL NEOPLASIA

Abnormal Pap Smear

> A 31-year-old woman is referred because of a Pap smear showing HSIL (high-grade squamous intraepithelial lesion). The patient states that her Pap smear three years ago was negative. She has been on combination steroid vaginal ring contraception for the past four years. Her cervix appears unremarkable on gross visual inspection.

Premalignant lesions of the cervix are usually **asymptomatic**. The progression from premalignant to invasive cancer has been reported to be approximately 8–10 years. Most lesions will spontaneously regress; others remain static, with only a minority progressing to cancer.

The **most common etiology** of cervical cancer is the human papilloma virus (HPV). More than 75 subtypes of HPV have been identified.

- HPV **16**, **18**, **31**, **33**, and **35** are the most common HPV types associated with **premalignant and cancerous lesions of the cervix**.
- HPV **6** and **11** are the most common HPV types associated with **benign condyloma acuminata**.

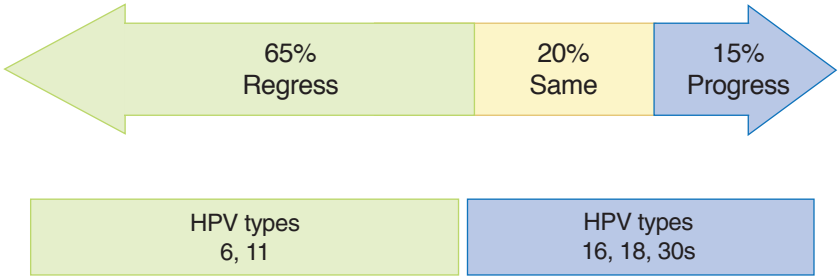


Figure II-4-2. Natural History of Cervical Dysplasia: Response to HPV Types

Risk factors include early age of intercourse, multiple sexual partners, cigarette smoking, and immunosuppression. The mediating factor for all these conditions is probably HPV.

Screening and performing of a Pap smear

Screening tests for premalignant cervical lesions include cytology and HPV-DNA typing. Cytologic screening uses the **Pap test**. The **most common site** for cervical dysplasia is the transformation zone (T-zone).

- **How is it performed?** Two specimens are obtained with the Pap smear: an ectocervical sample performed by scraping the T-zone with a spatula and an endocervical sample obtained with a cytobrush in a nonpregnant woman or a cotton-tip applicator in a pregnant woman.
- **What cytologic screening methods can be used?**
  - With the **conventional method**, the specimens are smeared onto a glass slide, which is placed in fixative and then microscopically examined.
  - With the **thin-layer, liquid-based cytology**, the specimens are rinsed into a preserving solution and then deposited on a slide as a thin layer of processed cells.
  - Both methods are equivalent for cancer screening but the liquid-based method has the advantage of doing reflex HPV-DNA typing.

Pap smear should be started at the following ages:

- **Age <21:** no Pap test or screening for HPV, regardless of sexual activity
- **Age 21:** Start Pap test with cytology alone without HPV testing; the recommendation is the same whether HPV vaccinated or not

The frequency of recommended Pap smear is as follows:

- **Age 21–29:** repeat Pap every 3 years with cytology alone; no HPV testing in this age group
- **Age 30–65:** repeat Pap every 3 years with cytology but no HPV testing **OR** repeat Pap every 5 years if both cytology and HPV testing (recommended option)

Pap smears should be discontinued:

- **After age 65** if negative cytology and/or HPV tests for past 10 years **AND** no history of CIN 2, CIN 3, or cervical carcinoma
- **Any age** if total hysterectomy **AND** no history of cervical neoplasia

Classification of a Pap smear

The **Bethesda system** is the current classification used in the United States.

- **Negative** for intraepithelial lesion or malignancy; comments may report trichomoniasis, candida, BV, HSV, or atrophy
- **Abnormal squamous cells** (99% of abnormal Pap smears)
  - **ASC-US (atypical squamous cells of undetermined significance):** changes suggestive of but not adequate to label LSIL
  - **LSIL (low-grade squamous intraepithelial lesion):** biopsy is expected to show histologic findings of HPV, mild dysplasia, or CIN 1
  - **ASC-H (atypical squamous cells can't rule out HSIL):** changes suggestive of but not adequate to label HSIL
  - **HSIL (high-grade squamous intraepithelial lesion):** biopsy is expected to show histologic findings of moderate–severe dysplasia, CIN 2, CIN 3, or CIS
  - **Squamous cell carcinoma:** biopsy is expected to show histologic findings of invasive cancer

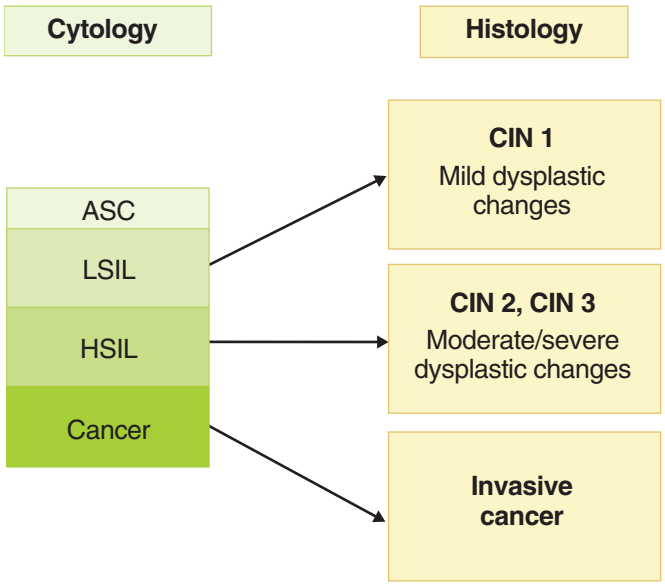


Figure II-4-3. Classification of Cervical Dysplasias

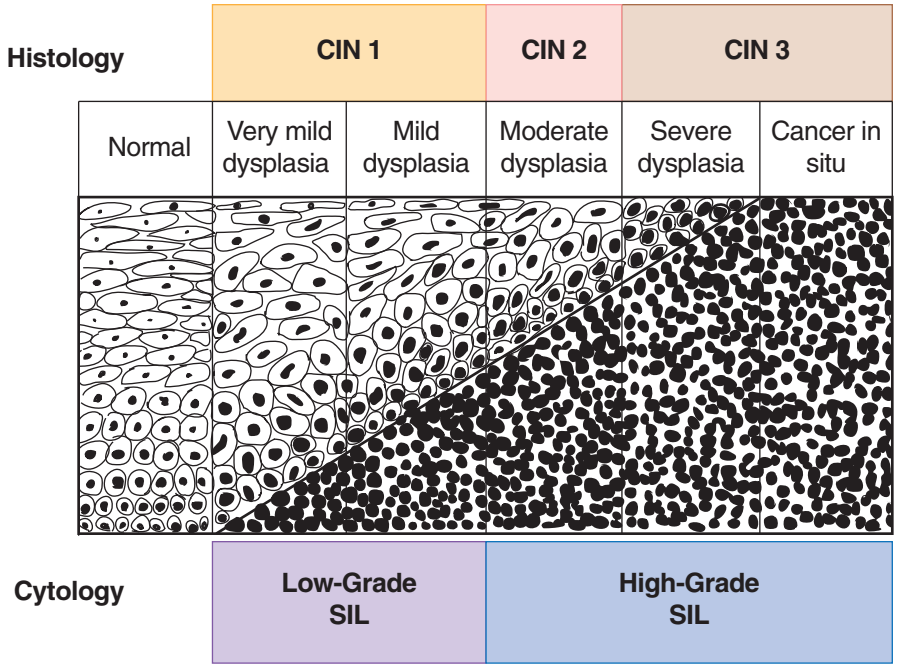


Figure II-4-4. Histologic Appearance of Cervical Dysplasia with Progressive Severity

Diagnostic approach to an abnormal Pap smear

- **Accelerated repeat Pap:** an option for findings of ASC-US in patients of any age, and the preferred option with either ASC-US or LSIL in patients age 21–24. Repeat the Pap in 12 months.

  - If repeat cytology is negative, repeat Pap in another 12 months.
  - If repeat cytology is anything other than negative, proceed to colposcopy and biopsies.
- **HPV DNA testing:** the preferred option for findings of ASC-US in patients age ≥25. It is acceptable but not preferred in patients ages 21–24.
  - If liquid-based cytology was used on the initial Pap, one can use this specimen for DNA testing.
  - If conventional methods were used, repeat a second Pap. Perform colposcopy only if high-risk HPV DNA is identified.
- **Colposcopy:** indicated for evaluation of LSIL in patients age ≥25 and all patients with ASC-H and HSIL. Colposcopy is a magnification of the cervix (10–12x); it is aided by acetic acid, which makes the vascular patterns more visible.
  - **Satisfactory or adequate** colposcopy is diagnosed if the entire T-zone is visualized and no lesions disappear into the endocervical canal.
  - **Unsatisfactory or inadequate** colposcopy is diagnosed if the entire T-zone cannot be fully visualized.
- **Endocervical curettage (ECC):** All nonpregnant patients undergoing colposcopy that shows metaplastic epithelium entering the endocervical canal will undergo an ECC to rule out endocervical lesions.
- **Ectocervical biopsy:** Lesions identified on the ectocervix by colposcopy (e.g., mosaicism, punctation, white lesions, abnormal vessels) are biopsied and sent for histology.
- **Compare Pap smear and biopsy:** When the biopsy histology is complete, it is compared with the level of Pap smear abnormality to ensure the level of severity is comparable.
- **Cone biopsy:** If the Pap smear is worse than the histology (suggesting the site of abnormal Pap smear cells was not biopsied), then a cone biopsy is performed. Other indications for conization of the cervix include abnormal ECC histology, a lesion seen entering the endocervical canal, and a biopsy showing microinvasive carcinoma of the cervix. Deep cone biopsies can result in an **incompetent cervix**. Another risk of cone biopsy is **cervical stenosis**.

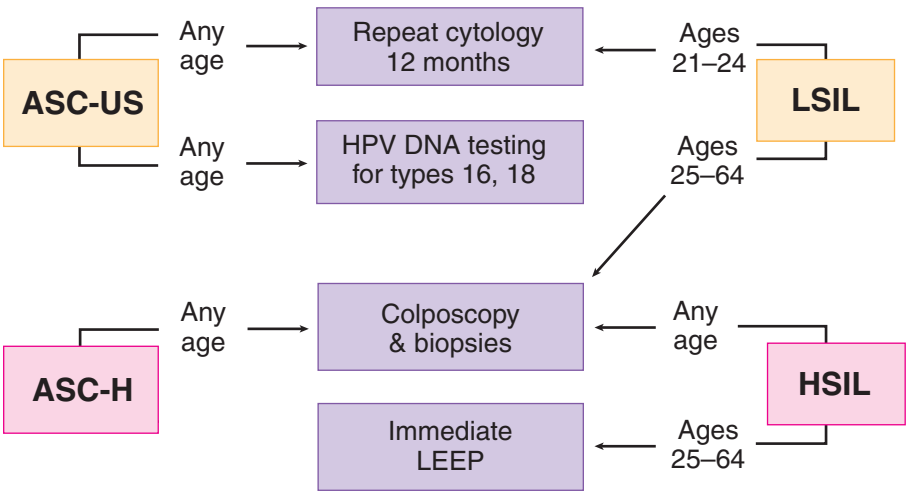


Figure II-4-5. Diagnostic Options for Abnormal Pap Smear (2013)

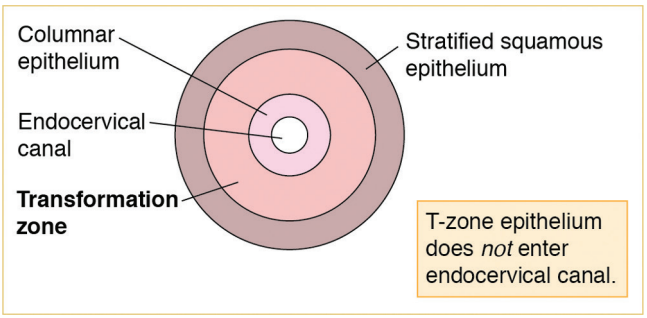


Figure II-4-6.
Cervical Dysplasia: Satisfactory Colposcopy

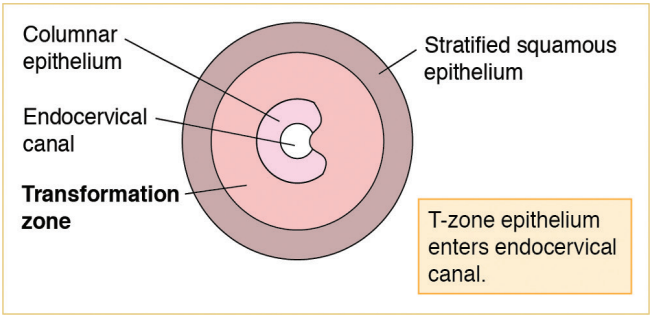


Figure II-4-7.
Cervical Dysplasia: Unsatisfactory Colposcopy

Management according to histology

- Observation and follow-up without treatment are appropriate for CIN 1 and include any of the following: repeat Pap in 6 and 12 months; colposcopy and repeat Pap in 12 months; or HPV DNA testing in 12 months.
- **Ablative modalities** can be used for CIN 1, 2, and 3 but are rarely used anymore. These include cryotherapy (freezing), laser vaporization, and electrofulguration.
- **Excisional procedures** can be used for CIN 1, 2, and 3. These include LEEP (loop electrosurgical excision procedure) or cold-knife conization.
- **Hysterectomy** is only acceptable with biopsy-confirmed, recurrent CIN 2 or 3.

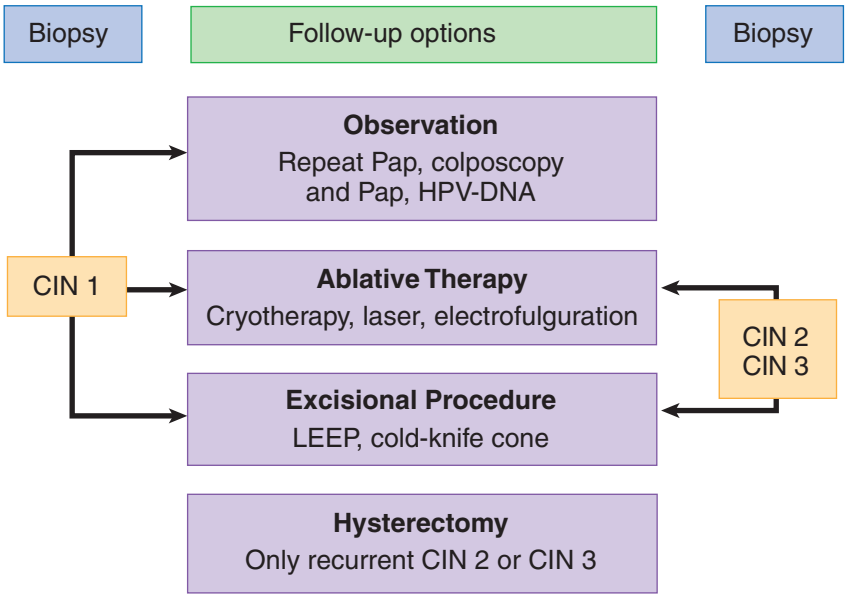


Figure II-4-8. Cervical Dysplasia: Management According to Histology

Follow-Up. Patients treated with either ablative or excisional procedures require follow-up repeat Pap smears, colposcopy and Pap smear, or HPV DNA testing every four to six months for two years.

Invasive Cervical Cancer

A 43-year-old woman complains of intermenstrual postcoital bleeding for the past six months between regular menstrual cycles that occur every 28 days. On pelvic examination a 3 cm exophytic mass is seen from the anterior lip of the cervix. The rest of the pelvic examination, including a rectovaginal examination, is normal.

Invasive cervical cancer is cervical neoplasia that has penetrated through the basement membrane. Patients can present with postcoital vaginal bleeding. Other symptoms include irregular vaginal bleeding and, in advanced stages, lower extremity pain and edema.

Cervical carcinoma is the **third most common gynecologic malignancy**; **45** is the mean age at diagnosis.

Diagnostic Tests/Findings.

- **Cervical biopsy.** The initial diagnostic test should be a cervical biopsy; the most common diagnosis is squamous cell carcinoma.
- **Metastatic workup.** Once a tissue diagnosis of invasive carcinoma is made, a metastatic workup should be done that includes pelvic examination, chest x-ray, intravenous pyelogram, cystoscopy, and sigmoidoscopy.
- **Imaging studies.** Invasive cervical cancer is the only gynecologic cancer that is staged clinically; an abdominal pelvic CT scan or MRI cannot be used for clinical staging.

Staging is **clinical** based on pelvic examination and may include an intravenous pyelogram (IVP), cystoscopy, or proctoscopy. It does not require surgical procedure other than a biopsy. **Stage 1** is the most common stage.

Management. Patients treated surgically are evaluated for risk factors for metastatic disease and tumor recurrence. These include metastatic disease to the lymph nodes, tumor size >4 cm, poorly differentiated lesions, or positive margins. Patients with these findings are offered adjuvant therapy (radiation therapy and chemotherapy).

Specific by stage:

- **Stage Ia1:** total simple hysterectomy, either vaginal or abdominal
- **Stage Ia2:** modified radical hysterectomy
- **Stage IB or IIA:** either radical hysterectomy with pelvic and paraaortic lymphadenectomy (if premenopausal) and peritoneal washings OR pelvic radiation (if postmenopausal); in those who can tolerate surgery, a radical hysterectomy is preferred, although studies have demonstrated equal cure rates with radiation or surgical treatment
- **Stage IIB, III, or IV:** radiation therapy and chemotherapy for all ages

Table II-4-1. Stage I—Most Common (Spread Limited to Cervix)

Ia1	• ≤3 mm • Minimal invasion	Total simple hysterectomy
Ia2	• >3 mm but ≤5 mm • Microinvasion	Modified radical hysterectomy
IB	• >5 mm • Frank invasion	Radical hysterectomy

All patients with invasive cervical cancer should be followed up with Pap smear every three months for two years after treatment, and then every six months for the subsequent three years.

- Patients who have a **local recurrence** can be treated with radiation therapy; if they had received radiation previously, they might be considered candidates for a pelvic exenteration.
- Patients with **distant metastases** should be considered for chemotherapy treatment. The most active chemotherapeutic agent for cervical cancer is cisplatinum.

Cervical Neoplasia in Pregnancy

A 25-year-old woman with intrauterine pregnancy at 14 weeks by dates is referred because of a Pap smear showing as HSIL (high-grade squamous intraepithelial lesion). On pelvic examination there is a gravid uterus consistent with 14 weeks size, and the cervix is grossly normal to visual inspection.

Diagnostic Tests/Findings.

- **Effect of pregnancy.** Pregnancy per se does not predispose to abnormal cytology and does not accelerate precancerous lesion progression into invasive carcinoma.
- **Colposcopy and biopsy.** A patient who is pregnant with an abnormal Pap smear should be evaluated in the same fashion as when in a nonpregnant state. An abnormal Pap smear is followed with colposcopy with the aid of acetic acid for better visualization of the cervix. Any abnormal lesions of the ectocervix are biopsied.
- **Perform an ECC?** Owing to increased cervical vascularity, ECC is not performed during pregnancy.

Management.

- **CIN.** Patients with intraepithelial neoplasia or dysplasia should be followed with Pap smear and colposcopy every three months during the pregnancy. At 6–8 weeks postpartum the patient should be reevaluated with repeat colposcopy and Pap smear. Any persistent lesions can be definitively treated postpartum.
- **Microinvasion.** Patients with microinvasive cervical cancer on biopsy during pregnancy should be evaluated with cone biopsy to ensure no frank invasion. If the cone biopsy specimen shows microinvasive carcinoma during pregnancy, these patients can also be followed conservatively, delivered vaginally, reevaluated, and treated two months postpartum.
- **Invasive cancer.** If the punch biopsy of the cervix reveals frankly invasive carcinoma, then treatment is based on the gestational age.
  - In general, if a diagnosis of invasive carcinoma is made **before 24 weeks** of pregnancy, the patient should receive definitive treatment (e.g., radical hysterectomy or radiation therapy).
  - If the diagnosis is made **after 24 weeks** of pregnancy, then conservative management up to about 32–33 weeks can be done to allow for fetal maturity to be achieved, at which time cesarean delivery is performed and definite treatment begun.

Prevention of Cervical Dysplasia by Vaccination

The 9 valent HPV recombinant vaccine [Gardasil-9] is recommended for all females age 9–45, with target age 11–12.

- The vaccine uses noninfectious particles to protect against 9 HPV types (6, 11, 16, 18, 31, 33, 45, 52, 58).
- Three doses are given: initial, then two months later, then six months later, for an approximate cost of $300.

Recommendations.

- Administer to all females age 9–45, with target age 11–12. Efficacy is highest before the patient's immune system has been presented with HPV.
- Testing for HPV is not recommended before vaccination. No easy method of identifying all HPV types is currently available.
- Continue regular Pap smears according to current guidelines because the vaccine does not prevent against all HPV types that can cause genital warts or cervical cancer.
- Sexually active women can receive the vaccine. Women with previous abnormal cervical cytology or genital warts also can receive the vaccine, but it may be less effective. It can be given to patients with previous CIN, but benefits may be limited.
- The vaccine is not recommended for pregnant or immunosuppressed women.

MÜLLERIAN ANOMALIES

Uterine anomalies (3% of fertile women, with normal reproductive outcomes) are classified into 7 types (per American Fertility Society 1988) based on the developmental problem responsible for the irregular shape.

Uterine anomalies may result from 3 mechanisms:

- **Stage 1:** failure of one or both of the 2 Müllerian ducts to form
- **Stage 2:** failure of the 2 ducts to fuse completely
- **Stage 3:** failure of the 2 fused Müllerian ducts to dissolve the septum that results from fusion

Failure to Form

Hypoplasia/agenesis

A woman may lack a vagina, a cervix (the bottom one-third of the uterus that opens into the vagina), the fallopian tubes, or the entire vagina and body of the uterus (except for the fundus). This occurs from a developmental problem with a section of both of the Müllerian ducts.

These anomalies are commonly associated with urinary tract anomalies because the structures that give rise to the urinary tract lie close to the Müllerian ducts and are affected by the same injurious insult.

Unicornuate uterus

When one of the Müllerian ducts fails to form, a single-horn (banana-shaped) uterus develops from the healthy Müllerian duct. This single-horn uterus may stand alone. However, in 65% of women with a unicornuate uterus, the remaining Müllerian duct may form an incomplete (rudimentary) horn.

There may be no cavity in this rudimentary horn or it may have a small space within it, but there is no opening that communicates with the unicornuate uterus and vagina.

- In the latter case, a girl may have monthly pain during adolescence because there is no outlet for the menses from this rudimentary horn. That pain would lead to identification of this problem.
- In some cases, the rudimentary horn contains a cavity that is continuous with the healthy single-horn uterus but is much smaller than the cavity within the healthy uterus.
- There is a risk that a pregnancy will implant in this rudimentary horn, but because of space limitations 90% of such pregnancies rupture.

Failure to Fuse

Didelphys uterus

A double uterus results from the complete failure of the 2 Müllerian ducts to fuse together (stage 1 of development). So each duct develops into a separate uterus, each narrower than a normal uterus and with only a single horn.

These 2 uteri may each have a cervix or they may share a cervix. In 67% of cases, a didelphys uterus is associated with 2 vaginas separated by a thin wall. Preterm delivery is common if pregnancy occurs in these patients.

Bicornuate uterus

Bicornuate uterus (most common congenital uterine anomaly [45%]) results from failure of fusion between the Müllerian ducts at the "top." This failure may be "complete," resulting in 2 separate single-horn uterine bodies sharing one cervix.

Alternatively, in a "partial" bicornuate uterus, fusion between the Müllerian ducts occurs at the "bottom" but not the "top." Thus, there is a single uterine cavity at the bottom with a single cervix, but it branches into 2 distinct horns at the top. Because the ducts never fuse at the top, these 2 horns are separate structures when seen from the outside of the uterus.

Preterm delivery and malpresentation are common with pregnancy.

Failure to Dissolve Septum

Septate uterus

A septate uterus results from a problem in stage 2 or 3 of uterine development. The two Müllerian ducts fuse normally; however, there is a failure in degeneration of the median septum.

- If the failure is "complete," a median septum persists in the entire uterus, separating the uterine cavity into 2 single-horned uteri that share one cervix.
- If the failure is "partial," resorption of the lower part of the median septum occurs in stage 2 but the top of the septum fails to dissolve in stage 3. Thus, there is a single cervix and uterine cavity at the bottom, but at the top that cavity divides into 2 distinct horns.

Because this uterine anomaly occurs later in uterine development after complete duct fusion, the external shape of the uterus is a normal-appearing single unit. This is distinct from the bicornuate uterus, which can be seen branching into 2 distinct horns when viewed from the outside.

Preterm delivery and malpresentation are common with pregnancy.

Arcuate uterus

This type of uterus is essentially normal in shape with a small midline indentation in the uterine fundus, which results from failure to dissolve the median septum completely. It is given a distinct classification because it seems to have no negative effects on pregnancy with regard to preterm labor or malpresentation.

DES uterus

The daughters of mothers exposed to diethylstilbestrol (DES) during pregnancy are predisposed to uterine abnormalities and clear cell carcinoma of the vagina.

- >70% have abnormalities, including a small, incompletely formed uterus ("hypoplastic") and/or a T-shaped cavity.
- 50% have cervical defects (e.g., an incompletely formed cervix that predisposes to cervical insufficiency).

The mechanism by which DES disrupts normal uterine development is not known.

ENLARGED UTERUS

Leiomyoma Uteri

Leiomyoma uteri is a benign smooth muscle growth of the myometrium (**most common benign uterine tumor**). It is 5 times more common in black women than white women.

Leiomyoma uteri can develop in a number of anatomic locations.

- **Intramural:** The **most common location** of a leiomyoma is within the wall of the uterus. When small it is usually asymptomatic and cannot be felt on examination, unless it enlarges to where the normal uterine external contour is altered.
- **Submucosal:** These myomas are located beneath the endometrium and can distort the uterine cavity. The distorted overlying endometrium may not respond appropriately to the normal hormonal fluctuations, resulting in unpredictable, often intermenstrual bleeding. Abnormal vaginal bleeding is the **most common symptom** of a submucosal myoma and can result in anemia. Menorrhagia is defined as heavy menses and metrorrhagia is defined as irregular bleeding in between menses. Menometrorrhagia consists of both heavy menses and bleeding in between the menses.
- **Subserosal:** These are located beneath the uterine serosa. As they grow they distort the external contour of the uterus causing the firm, nontender asymmetry. Depending on their location they can put pressure on the bladder, rectum, or ureters. If they are pedunculated, or attached to the uterus by a stalk, they can become parasitic fibroids. They break away from the uterus and receive their blood supply from another abdominal organ (such as the omentum or the mesentery of the intestine).

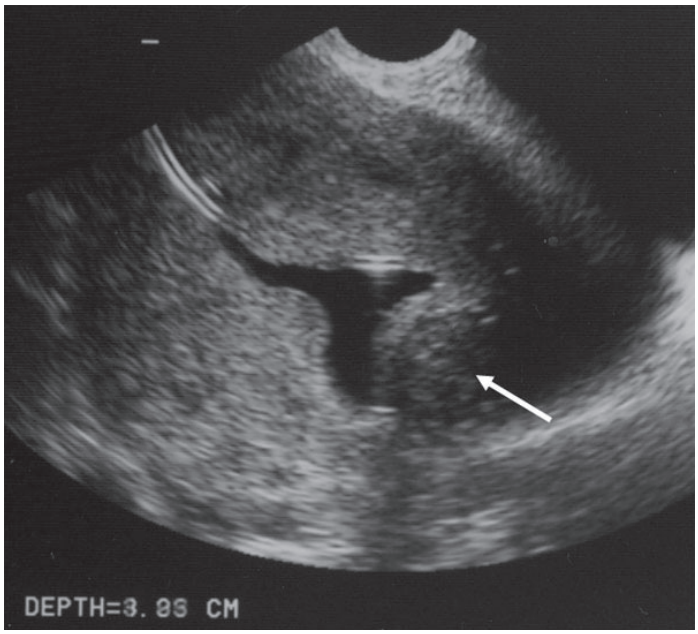


Figure II-4-9. Submucosal Leiomyoma

Changes in size are dependent on the reproductive life stage of the woman.

- **Slow growth:** Most leiomyomas are small, grow slowly, and cause no symptoms. Only when massive in size do they cause pelvic pressure symptoms.
- **Rapid growth:** Estrogen receptors are increased in leiomyomas, causing rapid enlargement during times of high estrogen levels, such as pregnancy.
- **Degeneration:** During times of rapid growth, myomas may outgrow their blood supply, resulting in ischemic degeneration of a fibroid. Common degenerations that are seen include hyaline, calcific, and red degeneration. The latter, also known as carneous degeneration, can cause such extreme, acute pain that the patient requires hospitalization and narcotics. This is **most common** during pregnancy.
- **Shrinkage:** When estrogen levels fall, with estrogen receptors no longer stimulated, leiomyomas will typically decrease in size. This predictably occurs after menopause but can also occur when estrogen levels are medically reduced through gonadotropin releasing hormone (GnRH) agonist suppression of follicle-stimulating hormone (FSH).

Diagnosis.

- **Pelvic examination:** In most cases the diagnosis is made clinically by identifying an enlarged, asymmetric, nontender uterus in the absence of pregnancy. The size of the fibroid is compared with the size of a pregnant uterus. A pregnant uterus that reaches the umbilicus is approximately 20 weeks in gestation; if the pregnant uterus reaches the symphysis pubis, it is approximately 12 weeks in gestation.
- **Sonography:** Traditional abdominal or vaginal ultrasound can image large intramural or subserosal myomas. Saline infusion sonography is helpful for identifying submucosal myomas by instilling 5–10 mL of saline into the uterine cavity before visualizing the uterine cavity with an endovaginal sonogram probe.
- **Hysteroscopy:** Submucosal myomas may be identified by visualizing them directly with hysteroscopy.
- **Histology:** The only definitive diagnosis is by surgical confirmation of excised tissue.

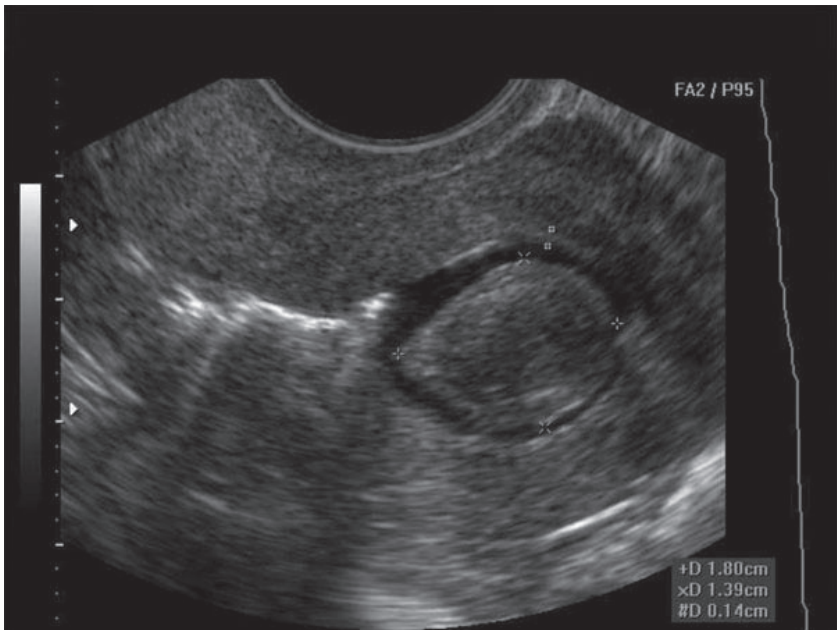


Figure II-4-10. Saline Ultrasonography Demonstrating an Intracavitary Leiomyoma

Management. Most leiomyomas can be **managed conservatively** and followed expectantly with regular pelvic examinations.

- **Presurgical shrinkage:** After 3–6 months of GnRH analog therapy, with resultant hypoestrogenic state, a 60–70% reduction in size of the fibroids can be expected. However, once the leuprolide (Lupron) is terminated, there will be a regrowth of the fibroid within 6 months. Thus, GnRH analogs cannot be used for definitive cure, but they can be used in the adjuvant setting with surgical therapy. If a myomectomy is done, a decrease in size will be associated with a decrease in blood loss, and if a hysterectomy is planned, then perhaps a vaginal instead of an abdominal hysterectomy can be performed.
- **Myomectomy** if patient wishes to maintain fertility. The uterus is incised and the myoma removed through either a laparoscopic or laparotomy approach. If the myomectomy incision entered the endometrial cavity, delivery of any subsequent pregnancy should be by cesarean section because of increased risk of scar rupture in labor.
- **Embolization:** an invasive radiology procedure in which a catheter is placed into the vessels supplying the myoma. Microspheres are injected, causing ischemia and necrosis of the myoma.
- **Hysterectomy:** If patient has completed her childbearing, definitive therapy is an abdominal or vaginal hysterectomy.

Table II-4-2. Management of Leiomyomas

Management	Clinical effect/Method of Treatment
Observation	Most Serial pelvic exams
Presurgical shrinkage	↓ size by 70% GnRH analog 3–6 months; regrowth after stopping
Myomectomy	Preserves fertility Laparotomy, laparoscopy
Embolization	Preserves uterus Invasive radiology
Hysterectomy	Fertility completed Total abdominal hysterectomy; total vaginal hysterectomy

Adenomyosis

A 42-year-old woman complains of increasing pain with her menstrual periods for the past 8 months. She also states her periods are getting heavier, leaving her tired and weak. She underwent a postpartum tubal ligation after her last child 10 years ago. She has been treated for chronic hypertension for the past 3 years. On pelvic examination her uterus is 12-week size, globular, soft, and tender. Rectovaginal examination is unremarkable.

Adenomyosis is the presence of ectopic endometrial glands and stroma located within the myometrium of the uterine wall. The **most common presentation** is diffuse involvement of the myometrium. The lesion is known as an **adenomyoma** if the involvement is focal, surrounded by a pseudocapsule.

In most cases the diagnosis is made clinically by identifying an enlarged, symmetric, tender uterus in the absence of pregnancy. The only definitive diagnosis is by histologic confirmation of the surgically excised tissue.

Table II-4-3. Differential Diagnosis for Enlarged Nonpregnant Uterus

Leiomyoma	Adenomyosis
Asymmetric	Symmetric
Firm	Soft
Nontender	Tender

The majority of women are asymptomatic. The most common symptoms are secondary dysmenorrhea and menorrhagia.

Examination reveals a uterus that is globular and diffusely up to 2–3 times the normal size. Tenderness is most common immediately before and during menses.

U/S study or MRI imaging shows a diffusely symmetrically enlarged uterus with cystic areas found within the myometrial wall.

Management. Medical treatment includes the levonorgestrel (LNG) intrauterine system (IUS), which may decrease heavy menstrual bleeding. Surgery in the form of hysterectomy is the definitive treatment.

ENDOMETRIAL NEOPLASIA

Postmenopausal Bleeding

> A 65-year-old patient complains of vaginal bleeding for three months. Her last menstrual period was at age 52. She has not taken any hormone replacement. She was diagnosed with type 2 diabetes 20 years ago and was treated with oral hypoglycemic agents. She has chronic hypertension, for which she is treated with oral antihypertensives. Her height is 62 inches and weight 200 lb. Physical examination is normal with a normal-sized uterus and no vulvar, vaginal, or cervical lesions.

Postmenopausal bleeding is any bleeding that occurs after menopause. A patient is considered to be in menopause after 3 continuous months of cessation of menses and elevated gonadotropins. Menopause usually occurs at around age 52.

Endometrial carcinoma is the **most common** gynecologic malignancy (1% of women), with age 61 the mean age at diagnosis. **Lynch syndrome**, an autosomally dominant disease, accounts for 2–5% of all endometrial carcinoma (mean age at diagnosis age 50). In women with Lynch, lifetime risk of endometrial cancer is 10–20 times the general population.

There is **no screening test**.

The **differential diagnosis** of postmenopausal bleeding includes endometrial carcinoma, vaginal or endometrial atrophy, and postmenopausal hormonal replacement therapy. Although the **most common** cause of postmenopausal bleeding is vaginal or endometrial atrophy, the most important diagnosis to rule out is endometrial carcinoma.

The mediating factor for most endometrial carcinomas appears to be unopposed estrogen. This results from excessive hyperstimulation of the endometrium without the stabilizing effect of progesterone.

Risk factors include **obesity**, **hypertension**, and **diabetes mellitus**. Other risk factors include tamoxifen, nulliparity, late menopause, and chronic anovulation conditions, such as PCO disease.

Diagnostic Tests: Endometrial biopsy or transvaginal ultrasound can be used as an initial test for evaluating the endometrium.

- **Endometrial sampling.** This office procedure has historically been the initial diagnostic test for postmenopausal bleeding, due to its high sensitivity, low complication rate, and low cost. It is ideal for global lesions but not very sensitive for diagnosing localized structural lesions such as polyps or submucous leiomyomas.

- **Transvaginal sonogram.** This is an acceptable alternative initial test for non-persistent minimal bleeding in non-obese women who are not on hormone replacement. A thin, homogenous endometrial stripe <5 mm can reasonably exclude endometrial carcinoma. A thicker endometrial stripe warrants further assessment with an endometrial sampling.
- **Hysteroscopy.** This procedure allows direct visualization of the endocervical canal and endometrial cavity. Endocervical or endometrial polyps, or submucous leiomyomas, can be removed at the time of the hysteroscopy.

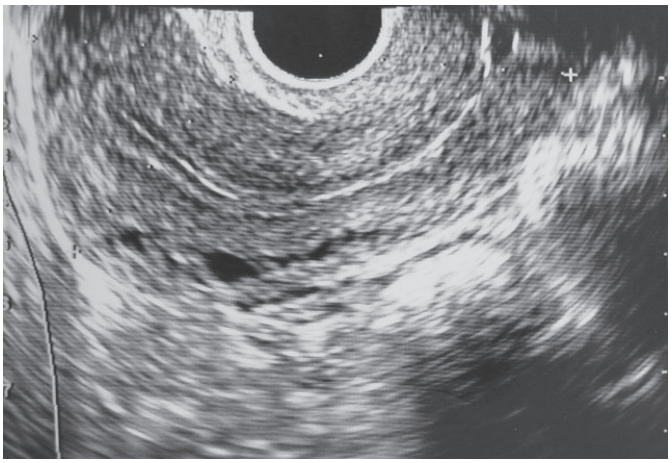


Figure II-4-11. Ultrasonography Demonstrating Normal Endometrial Stripe (<5 mm)

Staging

Staging is **surgical** and utilizes the **TNM** (tumor, nodes, metastasis) classification. **Stage 1 is the most common stage**.

Management. If the endometrial histology sampling reveals atrophy and no evidence of cancer, it can be assumed the patient is bleeding from atrophy and can be treated with hormone replacement therapy. With hormone replacement therapy, estrogen and progesterone should be given to the patient. If estrogen is given alone, the risk of endometrial cancer increases.

If the endometrial sampling reveals adenocarcinoma, the patient should be treated surgically.

- **Surgical therapy.** The mainstay of treatment of endometrial carcinoma is a total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO), pelvic and para-aortic lymphadenectomy, and peritoneal washings.
- **Radiation therapy.** An evaluation of the postoperative pathology report will classify patients into poor or good prognosis. Patients with poor prognosis should be considered for radiation therapy. Poor prognostic factors include metastasis to lymph nodes, >50% myometrial invasion, positive surgical margins, or poorly differentiated histology.
- **Chemotherapy.** Medical treatment is used for metastatic disease and involves **progestins** and cytotoxic agents.

Table II-4-4. Management of Endometrial Carcinoma

TAH-BSO: Basic Treatment for All Stages		
Stage I	TAH BSO Lymph node dissection	—
Stage II		Radiation
Stage III		Radiation, chemotherapy
Stage IV		

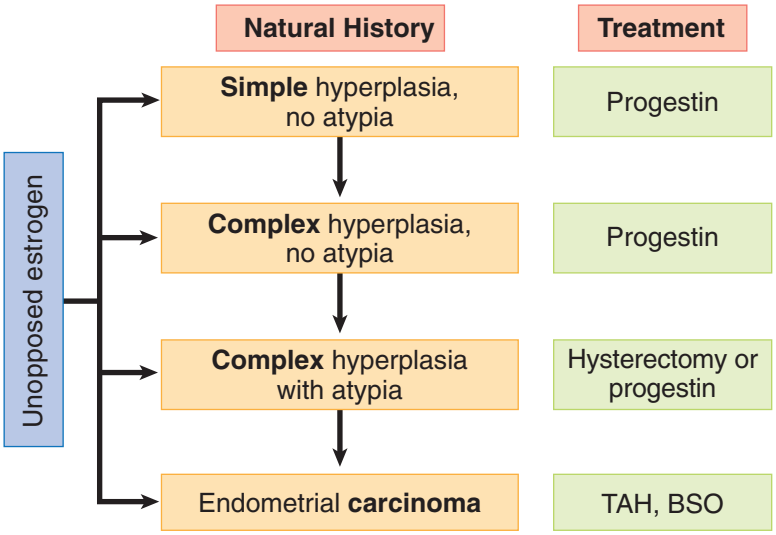


Figure II-4-12. Management of Endometrial Hyperplasia

Postmenopausal women taking estrogen replacement therapy must also be treated with progestins to prevent unopposed estrogen stimulation, which may lead to endometrial cancer. **Reproductive age women** with chronic anovulation (e.g., PCO syndrome) should also be treated with progestins to avoid endometrial hyperplasia from unopposed estrogen.

Disorders of the Ovaries and Oviducts

5

Learning Objectives

- ❑ Differentiate between physiologic enlargement of the adnexa and abnormal enlargement or painful adnexal mass
- ❑ List the causes of pelvic mass found prepubertal, premenopausal, and postmenopausal

PHYSIOLOGIC ENLARGEMENT

Functional Cysts

A 22-year-old woman comes for an annual examination and requests oral contraceptive pills. On pelvic examination a 6 cm mobile, smooth, soft, left adnexal mass is palpable. Endovaginal pelvic ultrasound shows a 6 cm, round, fluid-filled, simple ovarian cyst without septations or calcifications. She has no other significant personal or family history.

GYN Triad

Functional Ovarian Cyst

- Pelvic mass in reproductive years
- β-hCG (–)
- Sonogram: fluid-filled ovarian simple cyst

In the reproductive age years, the **most common cause** of a simple cystic mass is a physiologic cyst (luteal or follicular cyst). During those years the ovaries are functionally active, producing a dominant follicle (in the first half of the cycle) and a corpus luteum after ovulation (in the second half of the menstrual cycle). Either of these structures can become fluid-filled and enlarged, producing a functional cyst.

Differential Diagnosis.

- **Pregnancy: most common cause** of a pelvic mass in the reproductive years
- **Complex mass:** most common complex adnexal mass in young women is a **dermoid cyst** or **benign cystic teratoma**; other diagnoses include endometrioma, tubo-ovarian abscess, and ovarian cancer

Diagnosis.

- **Qualitative β-human chorionic gonadotropin (β-hCG) test.** If negative, this will rule out pregnancy.
- **Sonogram.** Physiological cysts will be simple, fluid-filled ovarian masses that are thin-walled, smooth, and mobile. A complex mass on ultrasound appearance is incompatible with a functional cyst.

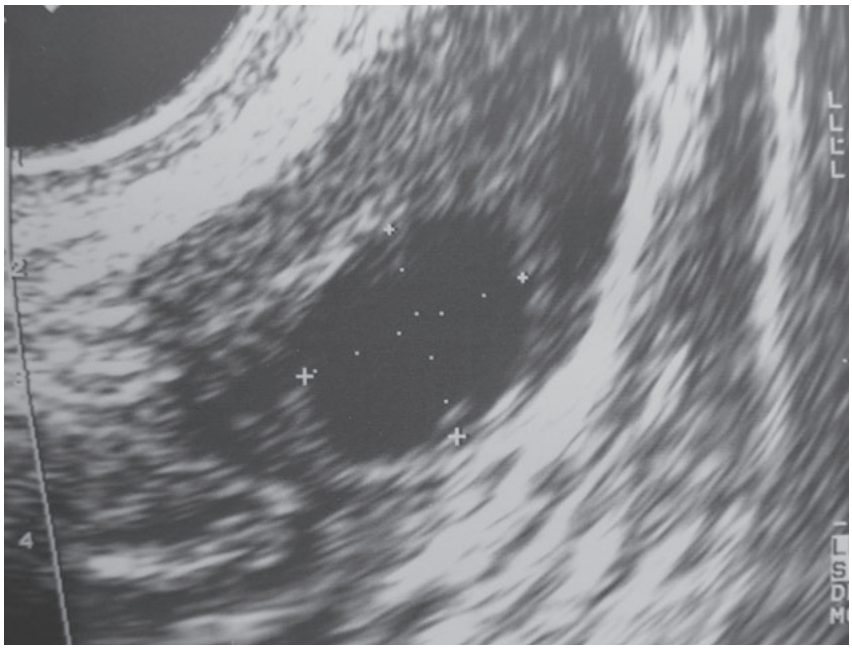


Figure II-5-1. Ultrasonographic Appearance of a Functional Cyst

Management. Most functional cysts can be managed expectantly, but surgery is indicated if certain characteristics are present.

- **Observation.** If the sonogram shows a simple cyst it is probably benign, but careful follow-up is needed. Follow-up exam should be in 6–8 weeks, at which time the functional cyst should have spontaneously resolved. During this period of observation the patient should be alerted to the possibility of acute onset of pain, which may be indicative of torsion of the adnexal cyst. Oral contraceptive medication can be used to help prevent further functional cysts from forming.
- **Laparoscopy.** Even if the cyst is simple in appearance, surgical evaluation should be performed if the cyst >7 cm or if patient had been on prior steroid contraception. Physiologic cysts do not usually get >7 cm in diameter. Functional cysts should not form if the patient has been on oral contraception for at least two months because gonadotropins should have been suppressed.

Polycystic Ovarian Syndrome

The ovaries are bilaterally enlarged with multiple peripheral cysts (20–100 in each ovary). This is due to high circulating androgens and high circulating insulin levels causing arrest of follicular development in various stages. This, along with stromal hyperplasia and a thickened ovarian capsule, results in enlarged ovaries bilaterally. PCOS is associated with **valproic acid** use. Management is conservative regarding ovaries.

For further discussion of PCOS pathophysiology and treatment, refer to Chapter 12, Hormonal Disorders.

Ovarian Hyperthecosis

In ovarian hyperthecosis, nests of luteinized theca cells are scattered in the ovarian stroma, rather than being confined to areas around cystic follicles (as in PCOS). Large amounts of androgens are produced, leading to increased peripheral estrone production and markedly increased risk of endometrial hyperplasia and carcinoma.

The clinical features are similar to those of PCOS; however, hirsutism is more severe and virilization is frequent.

- Patients present with anovulation, amenorrhea, or oligomenorrhea. Most patients will have severe insulin-resistance, with type 2 diabetes mellitus and cardiovascular disease.
- Unlike PCOS, which occurs only during the reproductive years, hyperthecosis of the ovaries can occur in postmenopausal women.

Management. Treatment is similar to that for hirsutism. Use oral contraceptive pills both to suppress androgen production (by reducing LH stimulation of the theca cells) and to decrease free androgens (by stimulating sex hormone-binding globulin).

Luteoma of Pregnancy

Luteoma of pregnancy is a rare, **non-neoplastic tumor-like mass** of the ovary that emerges during pregnancy and **regresses spontaneously** after delivery. It is usually **asymptomatic** and is found **incidentally** during a cesarean section or postpartum tubal ligation. It can be **hormonally active** and produce **androgens** resulting in maternal and fetal hirsutism and virilization.

Theca Lutein Cysts

These are **benign** neoplasms stimulated by **high levels of FSH and β-hCG**. They are **associated with twins** and **molar** pregnancies but they are only rarely associated with a normal singleton pregnancy. The **natural course** of these tumors is postpartum **spontaneous regression** and require only **conservative management**.

PREPUBERTAL PELVIC MASS

> An 8-year-old girl is evaluated in the emergency department for sudden onset of severe lower abdominal pain. A general surgery consult is obtained and appendicitis is ruled out. Pelvic ultrasound reveals a 7 cm solid and irregular right adnexal mass. Pelvic examination is consistent with a 7 cm right adnexal mass, and there is lower abdominal tenderness but no rebound present.

An adnexal mass in the prepubertal age group is abnormal. During the prepubertal and the postmenopausal years, functional ovarian cysts are not possible because ovarian follicles are not functioning. Therefore any ovarian enlargement is suspicious for neoplasm.

Sudden onset of acute abdominal pain is a typical presentation of germ cell tumors of the ovary. These tumors characteristically grow rapidly and give early symptomatology, as opposed to the epithelial cancers of the ovary that are diagnosed in advanced stages. Germ cell tumors of the ovary are **most common in young women** and present in early stage disease.

Differential Diagnosis. If sonography shows a complex adnexal mass in a girl or teenager, the possibility of **germ cell** tumors of the ovary has to be considered. The following serum **tumor markers** should be obtained: lactate dehydrogenase (LDH) for dysgerminoma, β-hCG for choriocarcinoma, and α-fetoprotein for endodermal sinus tumor.

Diagnosis. In a prepubertal patient who is symptomatic and has U/S evidence of an adnexal mass, a **surgical evaluation** is recommended.

- **Simple mass:** If the U/S shows the consistency of the mass to be simple (no septations or solid components), this mass can be evaluated through a laparoscopic approach.
- **Complex mass:** If the mass has septations or solid components, a laparoscopy or laparotomy should be performed, depending on the experience of the surgeon.

Table II-5-1. Prepubertal Pelvic Mass

Surgical diagnosis	Simple cyst	Laparoscopy
	Complex mass	Laparotomy
Management	Benign	Cystectomy Routine follow-up
	Malignant	Unilateral S&O Staging, chemotherapy
Prognosis	95% survival with chemotherapy	

Definition of abbreviations: S&O, Salpingo-oophorectomy.

Management.

- **Benign histology.** A cystectomy should be performed instead of a salpingo-oophorectomy. Because of the patient's age the surgical goal should be toward conservation of both ovaries. If the frozen section pathology analysis is benign, no further surgery is needed. Follow-up is on an annual basis.
- **Germ cell tumor.** A unilateral salpingo-oophorectomy and surgical staging (peritoneal and diaphragmatic biopsies, peritoneal cytology, pelvic and para-aortic lymphadenectomy, and omentectomy) should be done. All patients with germ cell tumors require postoperative chemotherapy. The most active regimens used are vinblastine, bleomycin, and cisplatin. Follow-up after conservative surgery is every three months with pelvic examination and tumor marker measurements.

The current survival rate is >95% in patients with germ cell tumors managed with conservative management and chemotherapy. Before the chemotherapy era, most patients succumbed to their disease.

PREMENOPAUSAL PELVIC MASS

Complex Mass

A 28-year-old woman is in the emergency department complaining of lower abdominal discomfort the last five days. She has no history of steroid contraceptive use. A year ago, her pelvic exam and Pap smear were negative. Pelvic exam today shows a 7 cm, mobile, painless right adnexal mass. An endovaginal sonogram in the emergency department confirms a 7 cm, mobile, irregular complex mass with prominent calcifications.

In young women, the **most common complex adnexal mass** is a dermoid cyst or benign cystic teratoma (discussed below). Other diagnoses include endometrioma, tubo-ovarian abscess, and ovarian cancer.

Differential diagnosis includes pregnancy and functional cysts.

Diagnosis. Qualitative **β-human chorionic gonadotropin** (**β-hCG**) test to rule out pregnancy; the appearance of a complex mass on U/S will rule out a functional cyst.

Management. Patients of reproductive age with a complex adnexal mass should be treated surgically (laparoscopy or laparotomy, depending on experience of the surgeon).

- **Cystectomy.** At the time of surgery an ovarian cystectomy should be attempted to preserve ovarian function in the reproductive age. Careful evaluation of the opposite adnexa should be performed, as dermoid cysts can occur bilaterally in 10–15% of cases.
- **Oophorectomy.** If an ovarian cystectomy cannot be done because of the size of the dermoid cyst, then an oophorectomy is performed, but conservative management should always be attempted before an oophorectomy is done.

Benign cystic teratoma

Dermoid cysts are benign tumors. They can contain cellular tissue from all 3 germ layers. The most common histology seen is ectodermal skin appendages (hair, sebaceous glands), thus the name "dermoid." Gastrointestinal histology can be identified, and carcinoid syndrome has been described originating from a dermoid cyst. Thyroid tissue can also be identified, and if it comprises >50% of the dermoid, then the condition of struma ovarii is identified.

Rarely, a malignancy can originate from a dermoid cyst, in which case the most common histology would be squamous cell carcinoma, which can metastasize.

GYN Triad

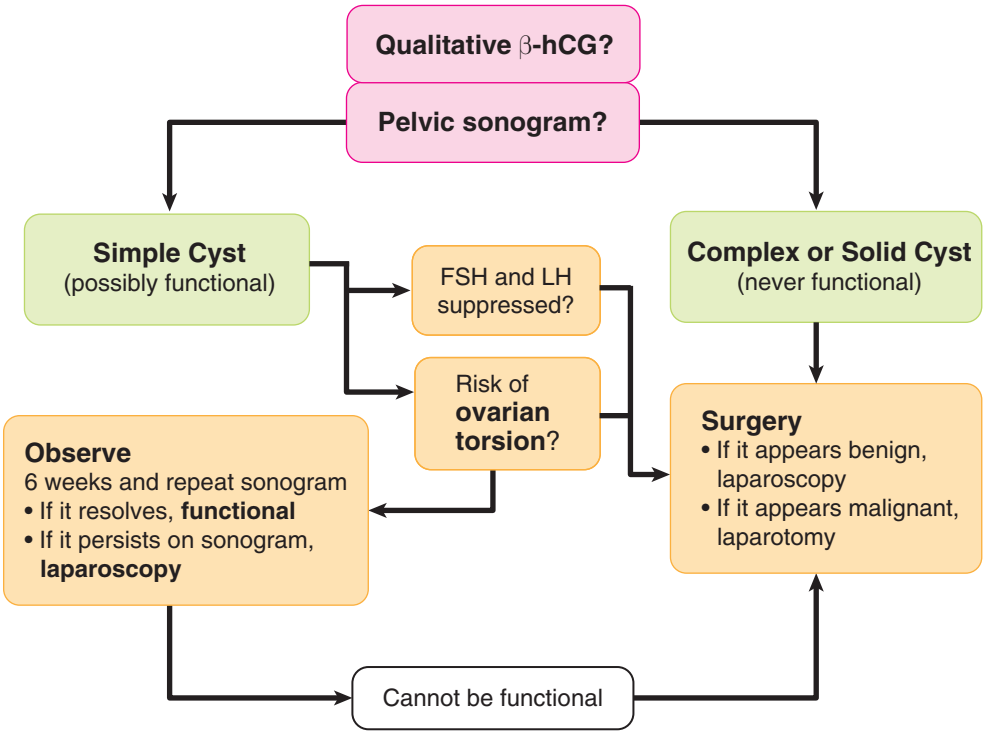
Dysgerminoma

- **Solid** pelvic mass in reproductive years
- β-hCG (–)
- ↑ LDH level

GYN Triad

Benign Cystic Teratoma

- Pelvic mass: reproductive years
- β-hCG (–)
- Sonogram: complex mass, calcifications



Used with permission: Elmar Sakala, MD

Figure II-5-2. Premenopausal Pelvic Mass

PAINFUL ADNEXAL MASS

A 31-year-old woman is taken to the emergency department complaining of severe sudden lower abdominal pain for approximately three hours. She was at work when she suddenly developed lower abdominal discomfort and pain, which got progressively worse. On examination the abdomen is tender, although no rebound tenderness is present, and there is a suggestion of an adnexal mass in the cul-de-sac area. Ultrasound shows an 8 cm left adnexal mass with a suggestion of torsion of the ovary.

GYN Triad

Ovarian Torsion

- Abrupt **unilateral** pelvic pain
- β-hCG (–)
- Sonogram: >7 cm adnexal mass

Sudden onset of severe lower abdominal pain in the presence of an adnexal mass is presumptive evidence of ovarian torsion.

Management. Untwist the ovary (with laparoscopy or laparotomy) and observe the ovary for a few minutes in the operating room to ensure revitalization. If revitalization occurs, an ovarian **cystectomy** can be performed with preservation of the ovary. If the ovary is necrotic, a unilateral **salpingo-oophorectomy** is performed.

Patients should have routine examination 4 weeks post-operation and then yearly. The pathology report should be checked carefully to confirm it is benign; if that is the case, go to routine follow-up.

POSTMENOPAUSAL PELVIC MASS

A 70-year-old woman comes for annual examination. She complains of lower abdominal discomfort; however, there is no weight loss or abdominal distention. On pelvic examination a nontender, 6 cm, solid, irregular, fixed, left adnexal mass is found. Her last examination one year ago was normal.

Postmenopausal pelvic mass is a pelvic mass identified after menopause. Ovaries in the postmenopausal age group should be atrophic; anytime they are enlarged the suspicion of **ovarian cancer** arises.

Ovarian carcinoma is the **second most common gynecologic malignancy**, with age 69 the mean age at diagnosis. It is the **most common gynecologic cancer** leading to death (1% of women die of ovarian cancer).

Diagnostic Tests.

- **GI tract lesions.** Abdominal pelvic CT scan or a pelvic U/S and GI studies (barium enema) to rule out any intestinal pathology such as diverticular disease
- **Urinary tract lesions.** IVP to identify any impingement of the urinary tract

There is currently **no screening test** for ovarian cancer. Pelvic U/S is excellent for finding pelvic masses, but is not specific for identifying which of these are benign. Only 3% of patients undergoing laparotomy for sonographically detected pelvic masses actually have ovarian cancer.

The most compelling theory of epithelial ovarian carcinogenesis suggests that serous, endometrioid, and clear cell carcinomas are derived from the fallopian tube and endometrium—not directly from the ovary.

Risk factors include **BRCA1 gene**, positive family history, high number of lifetime ovulations, infertility, and use of perineal talc powder. **Protective factors** include conditions that decrease the total number of lifetime ovulations.

- Removal or occlusion of the fallopian tubes: bilateral salpingectomy or tubal ligation
- Decreased lifetime ovulations: combination steroid contraception, chronic anovulation, breastfeeding, and short reproductive life

Classification of Ovarian Cancer.

- **Epithelial tumors** (80%) (**most common type** of histologic ovarian carcinoma) occur predominantly in postmenopausal women. These include serous, mucinous, Brenner, endometrioid, and clear cell tumors. The **most common** malignant epithelial cell type is **serous**.
- **Germ cell tumors** (15%) occur predominantly in teenagers. These include dysgerminoma, endodermal sinus tumors, teratomas, and choriocarcinoma. The **most common** malignant germ cell type is **dysgerminoma**. It is uniquely x-ray sensitive.
- **Stromal tumors** (5%) are functionally active. These include granulosa-theca cell tumors (which secrete estrogen and can cause bleeding from endometrial hyperplasia) and Sertoli-Leydig cell tumors (which secrete testosterone and can produce masculinization syndromes). Patients usually present with early stage disease and are treated either with removal of the involved adnexa (for those who desire further fertility) or a TAH and BSO (for those whose families have been completed). They metastasize infrequently and then require chemotherapy (vincristine, actinomycin, and Cytoxan).

GYN Triad

Serous Carcinoma

- Postmenopausal woman
- Pelvic mass
- ↑ CEA or CA-125 level

GYN Triad

Choriocarcinoma

- Postmenopausal woman
- Pelvic mass
- ↑ hCG level

GYN Triad

Sertoli-Leydig Tumor

- Postmenopausal pelvic mass
- Masculinization
- ↑ testosterone level

Table II-5-2. Classic Histology Types of Ovarian Cancer

Type	Percentage	Age Group
Epithelial	80%	Older
Germ cell	15%	Young
Stromal	5%	All

Metastatic tumors are cancers from a primary site other than the ovary. The **most common sources** are the endometrium, GI tract, and breast. **Krukenberg tumors** are mucin-producing tumors from the stomach or breast metastatic to the ovary.

GYN Triad

Endometrial Carcinoma Metastatic to Ovaries

- Postmenopausal woman with **bilateral** pelvic masses
- Postmenopausal bleeding
- Enlarged uterus

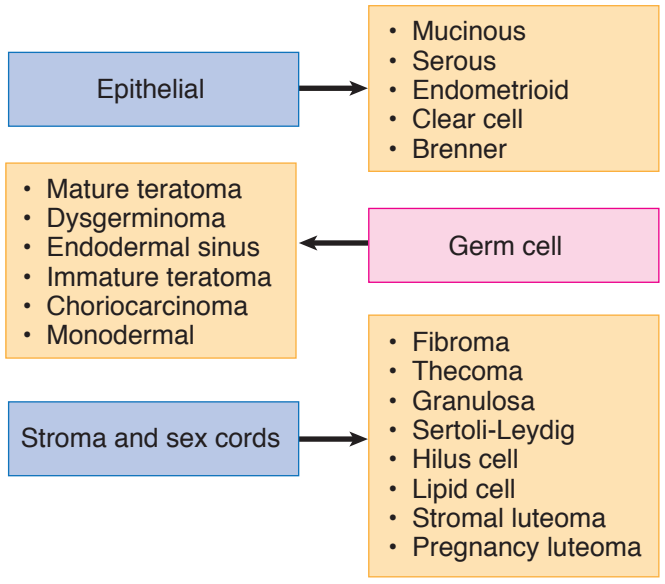


Figure II-5-3. Ovarian Oncology

Tumor Markers.

- **CA-125** (cancer antigen 125) and **CEA** (carcinoembryonic antigen) should be drawn for the possibility of ovarian epithelial cancer.
- **LDH, hCG**, and **α-fetoprotein** should be drawn for the possibility of germ cell tumors.
- **Estrogen** and **testosterone** should be drawn for the possibility of stromal tumors.

Staging. Staging is surgical.

Stage I: Spread limited to the **ovaries**
- IA. Limited to one ovary, capsule intact, negative cytology
- IB. Limited to both ovaries, capsules intact, negative cytology
- IC. One or both ovaries but ruptured capsule, positive cytology

Stage II: Extension to the **pelvis**
- IIA. Extension to uterus or tubes
- IIB. Extension to other pelvic structures

IIC. Extension to pelvis with positive cytology

Stage III: **Peritoneal** metastases or positive nodes. This is the **most common** stage at diagnosis.

IIIA. Microscopic peritoneal metastases

IIIB. Macroscopic peritoneal metastases ≤2 cm

IIIC. Macroscopic peritoneal metastases >2 cm

Stage IV: **Distant** metastases

IVA. Involves bladder or rectum

IVB. Distant metastasis

Management. Surgical exploration should follow preoperative studies and medical evaluation. If abdominal or pelvic CT scan shows no evidence of ascites or spread to the abdominal cavity and if the surgeon is an experienced laparoscopist, then the evaluation could be performed laparoscopically. At the time of surgery, a unilateral salpingo-oophorectomy (USO) is done and sent for frozen section.

- **Benign histology:** If the patient is not a good surgical candidate or the patient desires to maintain her uterus and contralateral ovary, a USO is sufficient treatment. If the USO by frozen section is benign and the patient is a good surgical candidate, then a TAH and BSO may be performed even though it is benign disease because the uterus and ovaries are not unusual sites of pathology in a woman.
- **Malignant histology:** In this case, a debulking procedure (cytoreduction) should be performed. This procedure consists of a TAH and BSO, omentectomy, and bowel resection, if necessary. Postoperative chemotherapy (carboplatin and Taxol) should be administered.

If the final pathology report of the enlarged adnexa was benign, the patient can be followed up in the office on a yearly basis for regular examination. If the pathology report was carcinoma, the patient can be followed up every three months for the first two years and then every six months for the next two years with follow-up of the CA-125 tumor marker.

Borderline Cancers. Another entity of ovarian cancer is the borderline tumors also known as tumors of low malignant potential. These are characterized by no invasion of the basement membrane and can also be treated conservatively.

- **Conservative surgery.** A patient who desires further fertility with a unilateral borderline cancer of the ovary can be treated with a USO with preservation of the uterus and the opposite adnexa.
- **Aggressive surgery.** If the patient has completed her family then the most acceptable treatment would be a TAH and BSO.
- **Chemotherapy.** Patients with borderline cancer of the ovary do not require chemotherapy unless they have metastasis; this is a rare occurrence.

Adnexal Mass with Ascites

A 65-year-old woman is referred for evaluation of abdominal distention and ascites and an adnexal mass. The patient has noted abdominal distention for the past six months, and on pelvic examination there is a 7 cm irregular and solid mass in the cul-de-sac, which is palpable by rectovaginal examination.

GYN Triad

Ovarian Carcinoma with Peritoneal Metastasis

- Postmenopausal bilateral pelvic masses
- Weight gain, anorexia
- Abdominal "shifting dullness"

Ascites is an abdominal accumulation of fluid in the peritoneal cavity, which usually causes abdominal distention. The etiology of ascites can be multifactorial and includes heart/kidney/liver disease and ovarian cancer.

In a female patient with ascites, ovarian carcinoma must always be considered. Although the etiology of ovarian carcinoma is not known, ovulation inhibition, as occurs with OCPs or pregnancy, does decrease the risk of epithelial ovarian cancer. **Meigs syndrome** is the triad of ascites, pleural effusion, and benign ovarian fibroma.

Lab abnormalities/diagnostic criteria. In a patient with an adnexal mass and ascites, an abdominal pelvic CT scan should be ordered for evaluation of the upper abdomen. The **most common method of ovarian carcinoma spread** is by peritoneal dissemination (exfoliation) and is commonly seen metastatic to the omentum and to the GI tract. The cause of death of patients with advanced ovarian carcinoma is bowel obstruction.

Management.

- **Surgical staging.** After an abdominal pelvic CT scan confirms the presence of ascites and the adnexal mass, an exploratory laparotomy and surgical staging should be performed. A salpingo-oophorectomy of the enlarged ovary should be done and sent for frozen section evaluation.
- **Debulking surgery.** If ovarian carcinoma is confirmed, then a debulking (cytoreductive) surgical procedure should be performed. This procedure usually includes a TAH, BSO, omentectomy, and, frequently, bowel resection.
- **Chemotherapy.** Postoperatively patients should be treated with six courses of a standard chemotherapy regimen, which includes Taxol and carboplatin. Patients are followed with the tumor marker CA-125.

Gestational Trophoblastic Neoplasia 6

Learning Objective

- ❑ Explain origin of gestational trophoblastic neoplasia

GESTATIONAL TROPHOBLASTIC NEOPLASIA

A 24-year-old Filipino nurse is 14 weeks pregnant by dates. She complains of vaginal bleeding as well as severe nausea and vomiting. Her uterus extends to her umbilicus but no fetal heart tones can be heard. Her blood pressure is 150/95 mm Hg. A dipstick urine shows 2+ proteinuria.

Gestational trophoblastic neoplasia (GTN), or **molar pregnancy**, is an abnormal proliferation of placental tissue involving both the cytotrophoblast and/or syncytiotrophoblast. **Classification** of GTN is done as follows:

- **Benign GTN** is the classic hydatidiform mole (H-mole). Incidence is 1:1200 in the U.S., but 1:120 in the Far East.
  - **Complete mole** (most common benign GTN) results from fertilization of an empty egg with a single X sperm resulting in paternally derived (androgenetic) **normal 46,XX** karyotype. No fetus, umbilical cord, or amniotic fluid is seen. The uterus is filled with grape-like vesicles composed of edematous avascular villi. Progression to malignancy is 20%.
  - **Incomplete mole** (less common) results from fertilization of a normal egg with 2 sperm resulting in **triploid 69,XXY** karyotype. A fetus, umbilical cord, and amniotic fluid is seen, which results ultimately in fetal demise. Progression to malignancy is 10%.
- **Malignant GTN** is the gestational trophoblastic tumor (**GTT**) which can develop in 3 categories.
  - **Non-metastatic disease** is localized only to the uterus. Cure rate is 100%.
  - **Good prognosis metastatic disease** has distant metastasis; the most common location is the pelvis or lung. Cure rate is >95%.
  - **Poor prognosis metastatic disease** has distant metastasis (most commonly brain or liver). Other poor prognosis factors are serum β-hCG levels >40,000, >4 months from the antecedent pregnancy, and following a term pregnancy. Cure rate is 65%.

GYN Triad

Molar Pregnancy

- Pregnancy <20 weeks
- HTN and proteinuria
- No fetal heart tones (FHT)

GYN Triad

Molar Pregnancy

- Pregnancy <20 weeks
- HTN and proteinuria
- Vaginal passage of vesicles

Note

Malignant GTN is characterized as localized or metastatic, and is classified as **good prognosis** or **poor prognosis**.

Table II-6-1. Benign Gestational Trophoblastic Neoplasia—H Mole

Complete	Incomplete
Empty egg	Normal egg
Paternal X's only	Maternal and paternal X's
46,XX (**di**ploidy)	69,XXY (**tri**ploidy)
Fetus absent	Fetus nonviable
20% → malignancy	10% → malignancy
No chemotherapy; serial β-hCG titers until (–); follow-up 1 year on oral contraceptive pill	

Table II-6-2. Malignant Gestational Trophoblastic Neoplasia

Nonmetastatic	Good Prognosis	Poor Prognosis
Uterus only	Pelvis or lung	Brain or liver
100% cure	>95% cure	65% cure
Single-agent chemotherapy		Multiple agent chemotherapy
1 year follow-up on oral contraceptive pill after β-hCG (–)		5 year follow-up on oral contraceptive pill

Risk factors. Increased prevalence **geographically** is most common in **Taiwan** and the **Philippines**. Other risk factors are maternal age extremes (age <20, age >35) and folate deficiency.

Clinical Findings.

- The **most common symptom** is bleeding prior to 16 weeks' gestation and passage of vesicles from the vagina. Other symptoms of a molar pregnancy include hypertension, hyperthyroidism, hyperemesis gravidarum, and no fetal heart tones appreciated.
- The **most common signs** are fundus larger than dates, absence of fetal heart tones, and bilateral cystic enlargements of the ovary known as **theca-lutein cysts**.
- The **most common site of distant metastasis** is the **lungs**.

Diagnosis. "**Snowstorm**" ultrasound. The diagnosis is confirmed with sonogram showing homogenous intrauterine echoes without a gestational sac or fetal parts.

Management. Baseline quantitative β-hCG titer; chest x-ray to rule out lung metastasis; and suction D&C to evacuate the uterine contents.

Place the patient on effective contraception (oral contraceptive pills) for the duration of the follow-up period to ensure no confusion between rising β-hCG titers from recurrent disease and normal pregnancy.

Table II-6-3. Gestational Trophoblastic Neoplasia—Basic Approach

β-hCG titer	Baseline for future comparison
Chest x-ray	Lung metastasis is ruled out
Suction D&C	Empty uterus contents
Oral contraceptive pills for 1 year	Prevent confusion: recurrent disease and normal pregnancy

Treatment is then based on histology and location of metastasis.

- **Benign GTN:** Weekly serial β-hCG titers until negative for 3 weeks, then monthly titers until negative for 12 months. **Follow-up is for 1 year**. If serial β-hCG titers plateau or rise and normal intrauterine pregnancy is ruled out by vaginal sonogram, patient is diagnosed with persistent gestational trophoblastic disease. Proceed with a metastatic workup (CT scan of the brain, thorax, abdomen, and pelvis) and manage as indicated below.
- **Non-metastatic or good prognosis metastatic disease: single agent** (**methotrexate** or actinomycin D) until weekly β-hCG titers become negative for 3 weeks, then monthly titers until negative for 12 months. **Follow-up is for 1 year**.
- **Poor prognosis metastatic disease: multiple agent** chemotherapy (which includes methotrexate, actinomycin-D, and cyclophosphamide until weekly β-hCG titers become negative for 3 weeks, then monthly titers for 2 years, then every 3 months for another 3 years. **Follow-up is for 5 years**.

Table II-6-4. Gynecologic Malignancy

Clinical staging	Cervical cancer
Surgical staging	Endometrial, ovarian, vulvar, and trophoblastic cancer

Sexually Transmitted Diseases 7

Learning Objectives

- ❑ Give an overview of the organisms involved in STDs
- ❑ Differentiate between STDs with and without ulcers
- ❑ Describe what is known about the sexual transmission of hepatitis B and HIV

SPECTRUM OF ORGANISMS

Bacterial organisms include chancroid, lymphogranuloma venereum, granuloma inguinale, chlamydia, gonorrhea, and syphilis.

Viral organisms include condyloma acuminatum, herpes simplex, hepatitis B virus, and human immunodeficiency virus.

Protozoan organisms include trichomoniasis.

STDs WITH ULCERS

Herpes Simplex Virus (HSV)

Refer to Obstetrics, Chapter 7, Perinatal Infections.

Syphilis

Refer to Obstetrics, Chapter 7, Perinatal Infections.

Chancroid

Chancroid is caused by *Haemophilus ducreyi*, a gram-negative bacterium. It is uncommon in the United States. It is a cofactor for HIV transmission.

Chancroid is one of two STDs which present with a **painful ulcer**. A pustule, usually on the vulva, becomes a painful ulcer within 72 hours, with a typically "ragged edge."

Diagnosis. A positive culture confirms the diagnosis, although a diagnosis is often made clinically after excluding syphilis and genital herpes.

Management. Single oral dose of azithromycin, single IM dose of ceftriaxone, or oral erythromycin base for seven days (CDC-recommended treatment).

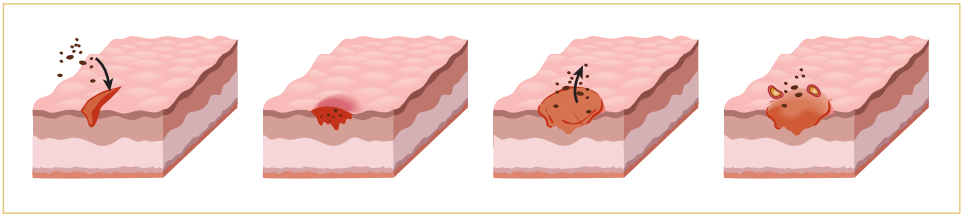


Figure II-7-1. Pathophysiology of Chancroids

Lymphogranuloma Venereum

Lymphogranuloma venereum (LGV) is caused by the L serotype of *Chlamydia trachomatis*. It is uncommon in the United States. The initial lesion is a **painless** ulcer.

A painless vesiculopustular eruption, usually on the vulva, spontaneously heals. This is replaced within a few weeks by perirectal adenopathy that can lead to abscesses and fistula formation.

The classic clinical lesion is a double genitocrural fold, the "groove sign."

Diagnosis. A positive culture of pus aspirated from a lymph node confirms the diagnosis.

Management. Oral doxycycline or erythromycin for three weeks (CDC-recommended treatment).

Granuloma Inguinale (Donovanosis)

This disease is caused by *Calymmatobacterium granulomatis*, a gram-negative intracellular bacterium. It is uncommon in the United States. The initial lesion is a **painless** ulcer.

A vulvar nodule breaks down, forming a painless, beefy red, highly vascular ulcer with fresh granulation tissue without regional lymphadenopathy. Lymphatic obstruction can result in marked vulvar enlargement. Chronic scarring can lead to lymphatic obstruction.

Diagnosis. Culture of the organism is difficult, but microscopic examination of an ulcer smear will reveal Donovan bodies.

Management. Oral doxycycline or azithromycin for three weeks (CDC-recommended treatment)

Table II-7-1. Comparison of STDs

With Ulcers	No Ulcers	Painful Ulcers
Chancroid	Chlamydia	Chancroid
Granuloma inguinale	HPV	Genital herpes
Genital herpes	Gonorrhea	
LGV	Hepatitis B	
Syphilis	HIV	

Table II-7-2. Comparison of STDs with Ulcers

Chancroid (painful)	Ragged, soft edge inflamed
LGV	Groove sign
Granuloma inguinale	Beefy red; Donovan bodies
Syphilis	Rolled, hard edge
Herpes (painful)	Smooth edge inflamed

STDs WITHOUT ULCERS

Condyloma Acuminatum

Condyloma acuminatum is caused by the **human papilloma virus** (HPV). It is the **most common overall STD in women**, as well as the most common viral STD. Transmission can occur with subclinical lesions. HPV subtypes 16 and 18 are associated with cervical and vulvar carcinoma, whereas condyloma is associated with HPV types 6 and 11. Predisposing factors include immunosuppression, diabetes, and pregnancy.

HPV is subclinical in most infected women. Symptoms of pain, odor, or bleeding occur only when lesions become large or infected. Clinical lesions are found in only 30% of infected women.

The characteristic appearance of a condyloma is a **pedunculated, soft papule that progresses into a cauliflower-like mass**. The most common site of lesions is the cervix.

Diagnosis. The lesions have an appearance so characteristic that biopsy is seldom necessary.

Management. Topical or local. Systemic therapy is not available.

- **Patient-applied topical treatment:** podofilox [Condylox] solution or gel (antimitotic drug), imiquimod [Aldara] cream (topically active immune-enhancer), or sinecatechins ointment (green-tea extract)
- **Provider-administered local treatment:** cryotherapy (liquid nitrogen or CryoProbe), podophyllin resin (not used in pregnancy), trichloroacetic acid [TCA] or bichloroacetic acid [BCA] (caustic agents), or surgical removal

Trichomonas Vaginitis

Refer to Gynecology, Chapter 3, Disorders of the Vagina and Vulva.

Chlamydia

Chlamydia is caused by *Chlamydia trachomatis*, an obligatory intracellular bacterium. It is the **most common bacterial STD** in women, occurring up to five times more frequently than gonorrhea. The long-term sequelae arise from pelvic adhesions, causing chronic pain and infertility. When the active infection ascends to the upper genital tract and becomes symptomatic, it is known as acute pelvic inflammatory disease (**acute PID**). Transmission from an infected gravida to her newborn may take place at delivery, causing conjunctivitis and otitis media.

Most chlamydial cervical infections, and even salpingo-oophoritis, are asymptomatic.

The classic cervical finding is mucopurulent cervical discharge. Urethral and cervical motion tenderness may or may not be noted.

Diagnosis. Nucleic acid amplification test (NAAT) of either cervical discharge or urine is used.

Management. Single oral dose of azithromycin or oral doxycycline for seven days (CDC-recommended treatment). Patients should avoid coitus for seven days after therapy. A test-of-cure (repeat testing 3–4 weeks after completing therapy) is recommended for pregnant women.

Gonorrhea

Gonorrhea is caused by *Neisseria gonorrhoeae*, a gram-negative diplococcus. The long-term sequelae arise from pelvic adhesions, causing chronic pain and infertility. When the active infection becomes symptomatic, it is known as acute pelvic inflammatory disease (**acute PID**). Systemic infection can occur.

Lower genital tract infection may lead to vulvovaginal discharge, itching, and burning with dysuria or rectal discomfort. **Upper genital tract infection** leads to bilateral abdominal-pelvic pain. Disseminated gonorrhea is characterized by dermatitis, polyarthralgia, and tenosynovitis.

Vulvovaginitis is seen on inspection. Mucopurulent cervical discharge is seen on speculum exam. Cervical motion tenderness is common with bimanual pelvic exam. Petechial skin lesions, septic arthritis, and, rarely, endocarditis or meningitis, may demonstrate with disseminated gonorrhea.

Diagnosis. Nucleic acid amplification test (NAAT) of either cervical discharge or urine is used.

Management. Single dose of IM ceftriaxone plus a single oral dose of azithromycin (CDC recommends dual therapy for gonococcus and chlamydia because of the frequency of coinfection). A Bartholin abscess needs to undergo incision and drainage with a Word catheter.

HEPATITIS B VIRUS (HBV)

Refer to Obstetrics, Chapter 7, Perinatal Infections.

HUMAN IMMUNODEFICIENCY VIRUS (HIV)

Refer to Obstetrics, Chapter 7, Perinatal Infections.

Pelvic Pain 8

Learning Objectives

- ❏ Provide an overview of the diagnosis and treatment of pelvic inflammatory disease
- ❏ Differentiate primary and secondary dysmenorrhea

PELVIC INFLAMMATORY DISEASE

A 19-year-old nulligravida presents to the emergency department with bilateral lower abdominal pelvic pain. The onset was 24 hours ago after she had just finished her menstrual period. She is sexually active but using no contraception. Speculum examination reveals mucopurulent cervical discharge. Bimanual pelvic examination shows bilateral adnexal tenderness and cervical motion tenderness. She is afebrile. Qualitative urinary β-hCG test is negative. Complete blood cell count shows WBC 14,000. ESR is elevated.

Pelvic inflammatory disease (PID) is a nonspecific term for a **spectrum of upper genital tract conditions** ranging from acute bacterial infection to massive adhesions from old inflammatory scarring.

The **most common** initial organisms are **chlamydia** and **gonorrhea**. With persistent infection, secondary bacterial invaders include anaerobes and gram-negative organisms.

PID is an ascending infection that starts within the cervix and moves up to involve the oviducts and ovaries.

- **Cervicitis:** The initial infection starts with invasion of endocervical glands with chlamydia and gonorrhea. A mucopurulent cervical discharge or friable cervix may be noted. Cervical cultures will be positive, but symptoms are usually absent.
- **Acute salpingo-oophoritis:** Usually after a menstrual period with breakdown of the cervical mucus barrier, the pathogenic organisms ascend through the uterus causing an endometritis; then the bacteria enter the oviduct where acute salpingo-oophoritis develops.
- **Chronic PID:** If the salpingo-oophoritis is not appropriately treated, the body's immune defenses will often overcome the infection but at the expense of persistent adhesions and scarring.
- **Tubo-ovarian abscess (TOA):** If the body's immune defenses cannot overcome the infection, the process worsens, producing an inflammatory mass involving the oviducts, ovaries, uterus, bowel, and omentum.

Risk Factors. The **most common** risk factor is female sexual activity in adolescence, with multiple partners. PID is increased in the month after insertion of an IUD, but this is probably exacerbation of preexisting subclinical infection.

Cervicitis

Often there are no symptoms except vaginal discharge. The **most common finding** is mucopurulent cervical discharge or a friable cervix. No pelvic tenderness is noted. The patient is afebrile.

Investigative findings can be a lab diagnosis or a clinical diagnosis. See Diagnosis section for chlamydia. WBC and ESR are normal.

Management. Single dose orally of cefixime and azithromycin.

GYN Triad

Acute Salpingo-Oophoritis

- **Bilateral** abdominal/pelvic pain
- Mucopurulent cervical discharge
- Cervical motion tenderness

Acute Salpingo-Oophoritis

Bilateral lower abdominal-pelvic pain may be variable, ranging from minimal to severe. Onset may be gradual to sudden, often after menses. Nausea and vomiting may be found if abdominal involvement is present.

On examination, mucopurulent cervical discharge, cervical-motion tenderness, and bilateral adnexal tenderness are present. Fever, tachycardia, abdominal tenderness, peritoneal signs, and guarding may be found depending on the extent of infection progression.

Investigative findings include elevated WBC and ESR. Pelvic sonography is usually unremarkable. Laparoscopy will show erythematous, edematous, purulent oviducts. Cervical cultures will come back positive for chlamydia or gonorrhea.

Differential diagnosis includes adnexal torsion, ectopic pregnancy, endometriosis, appendicitis, diverticulitis, Crohn disease, and ulcerative colitis.

Diagnosis. This is a made on **clinical grounds** using the following:

- **Minimal criteria:**
  - Sexually active young woman
  - Pelvic or lower abdominal pain
  - Tenderness: cervical motion or uterine or adnexal
- **Supportive criteria (but not necessary for diagnosis):**
  - Oral temperature >38.3 C (>101 F)
  - Abnormal cervical or vaginal mucopurulent discharge
  - Presence of abundant WBC on vaginal fluid saline microscopy
  - Elevated erythrocyte sedimentation rate
  - Positive lab findings of cervical *N. gonorrhoeae* or *C. trachomatis*
- **Most specific criteria for diagnosis:**
  - Endometrial biopsy showing endometritis
  - Vaginal sono or MRI imaging showing abnormal adnexa
  - Laparoscopic abnormalities consistent with PID

Management is often based on a presumptive diagnosis. Empiric broad spectrum coverage need to include *N. gonorrhoeae* or *C. trachomatis* as well as anaerobes (e.g., *B. fragilis*).

- **Outpatient treatment** is equivalent to inpatient in mild to moderate cases.
  - **Criteria:** absence of inpatient criteria
  - **Antibiotics:** ceftriaxone IM x 1 plus doxycycline po bid for 14 days with/without metronidazole po bid for 14 days

- **Inpatient treatment** is essential with severe cases.
  - **Criteria:** cannot rule out; failed outpatient therapy; unable to tolerate oral medications; severe illness, high fever, nausea/vomiting; tubo-ovarian abscess or pregnancy
  - **Antibiotics:** (1) cefotetan IV 12 h plus doxycycline po or IV q 12 h or (2) clindamycin plus gentamicin IV q 8 h

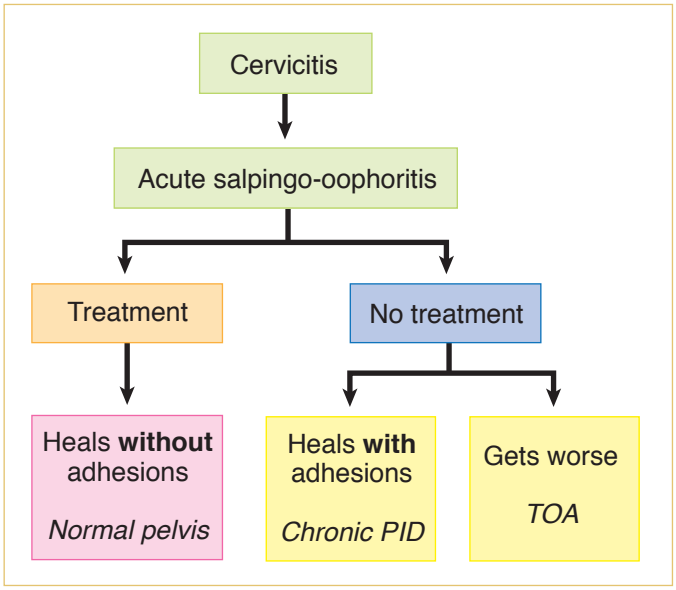


Figure II-8-1. Pelvic Inflammatory Disease

Tubo-Ovarian Abscess

Tubo-ovarian abscess (TOA) is the accumulation of pus in the adnexa forming an inflammatory mass involving the oviducts, ovaries, uterus, or omentum. The typical clinical presentation is similar to severe acute PID with acute pain, fever, chills, and vaginal discharge; some patients present with chronic pain and are afebrile.

The patient will look septic. Lower abdominal-pelvic pain is severe. Often there is severe back pain, rectal pain, and pain with bowel movements. Nausea and vomiting are present.

On examination the patient appears gravely sick. She has high fever with tachycardia. She may be in septic shock with hypotension. Abdominal examination shows peritoneal signs, guarding, and rigidity. Pelvic examination may show such severe pain that a rectal examination must be performed. Bilateral adnexal masses may be palpated.

Investigative findings include positive cervical cultures for chlamydia or gonorrhea. Blood cultures may be positive for gram-negative bacteria and anaerobic organisms such as *Bacteroides fragilis*. Culdocentesis may yield pus. WBC and ESR are markedly elevated. Sonography or CT scan will show bilateral complex pelvic masses.

Differential diagnosis includes septic abortion, diverticular or appendiceal abscess, and adnexal torsion.

Management. Inpatient IV clindamycin and gentamicin should result in fever defervescence within 72 hours. If there is no response or there is rupture of the abscess exposing free pus into the peritoneal cavity, significant mortality can occur. Exploratory laparotomy with possible TAH and BSO or percutaneous drainage through a colpotomy incision may be required.

GYN Triad

Chronic Salpingo-Oophoritis

- **Bilateral** abdominal/pelvic pain
- No cervical discharge
- Cervical motion tenderness

Chronic PID

Chronic bilateral lower abdominal-pelvic pain is present, varying from minimal to severe. Other symptoms may include history of infertility, dyspareunia, ectopic pregnancy, and abnormal vaginal bleeding. Nausea and vomiting are absent.

On examination, bilateral adnexal tenderness and cervical-motion tenderness is present, but mucopurulent cervical discharge is absent. Fever and tachycardia are absent.

Investigative findings include negative cervical cultures with normal WBC and ESR. Sonography may show bilateral cystic pelvic masses consistent with hydrosalpinges.

Diagnosis. Diagnosis is based on laparoscopic visualization of pelvic adhesions.

Management. Outpatient mild analgesics for pain. Lysis of tubal adhesions may be helpful for infertility. Severe unremitting pelvic pain may require a pelvic clean-out (TAH, BSO). If the ovaries are removed, estrogen replacement therapy is indicated.

PRIMARY DYSMENORRHEA

A 15-year-old girl comes to the outpatient office complaining of severe menstrual-period pain that started six months ago. Onset of menarche was age 13. The pain can be so severe that she is unable to attend school or carry on normal activities. She describes it as cramping in nature, and it is associated with nausea, vomiting, and diarrhea. When her menses are completed, the pain is gone. She is not sexually active. General exam is normal for age. Pelvic exam is unremarkable.

Note

Secondary dysmenorrhea refers to painful menstruation in the presence of pelvic pathology. It is more common among women in decades 4 and 5.

Primary dysmenorrhea refers to recurrent, crampy lower abdominal pain, along with nausea, vomiting, and diarrhea that occurs during menstruation in the absence of pelvic pathology. It is the **most common gynecologic complaint** among adolescent girls.

- Onset of pain generally does not occur until ovulatory menstrual cycles are established. Maturation of the hypothalamic-pituitary-gonadal axis leading to ovulation occurs in half of teenagers within 2 years postmenarche, and the majority of the remainder by 5 years postmenarche.
- Symptoms typically begin several hours prior to the onset of menstruation and continue for 1–3 days.
- Severity can be categorized by a grading system based on the degree of menstrual pain, presence of systemic symptoms, and impact on daily activities.

Pathogenesis.

- Symptoms appear to be caused by excess production of endometrial **prostaglandin** $F_{2\alpha}$ resulting from the spiral arteriolar constriction and necrosis that follow progesterone withdrawal as the corpus luteum involutes. The prostaglandins cause dysrhythmic uterine contractions, hypercontractility, and increased uterine muscle tone, leading to **uterine ischemia** that causes severe crampy lower abdominal pain.
- The effect of the prostaglandins on the gastrointestinal smooth muscle also can account for nausea, vomiting, and diarrhea via stimulation of the gastrointestinal tract.

Management. Suppression of prostaglandins is the objective of treatment, with NSAIDs (e.g., prostaglandin synthetase inhibitors) the first choice and continuous combination estrogen-progesterone steroid agents (e.g., oral contraceptives) the second choice.

GYN Triad

Endometriosis

- Chronic pelvic pain
- Painful intercourse
- Painful bowel movements

SECONDARY DYSMENORRHEA

Endometriosis

> A 34-year-old woman complains of painful periods, painful sex, painful bowel movements, and infertility for 2 years. She had used combination oral contraceptive pills from age 25–30. Pelvic examination reveals a tender, 5 cm cul-de-sac mass, along with tenderness and nodularity of the uterosacral ligaments.

Endometriosis is a benign condition in which endometrial glands and stroma are seen outside the endometrial cavity. While it is associated with increased risks of epithelial ovarian carcinoma, it is not a premalignant condition. Although the etiology is not known, the most accepted theory of explanation is that of Sampson, which is **retrograde menstruation**.

- The **most common site** of endometriosis is the ovary; because this is functioning endometrium, it bleeds on a monthly basis and can create adnexal enlargements known as endometriomas, also known as a **chocolate cyst**.
- The **second most common site** of endometriosis is the **cul-de-sac**, and in this area the endometriotic nodules grow on the uterosacral ligaments, giving the characteristic **uterosacral ligament nodularity** and tenderness appreciated by rectovaginal examination. Menstruation into the cul-de-sac creates fibrosis and adhesions of bowel to the pelvic organs and a rigid cul-de-sac, which accounts for **dyspareunia**.

Pelvic-abdominal pain is not necessarily related to the extent of disease. Painful intercourse (**dyspareunia**) is often experienced along with painful bowel movements (dyschezia). Infertility of endometriosis is not necessarily related to the extent of disease.

On examination, pelvic tenderness is common. A fixed, retroverted uterus is often caused by cul-de-sac adhesions. Uterosacral ligament nodularity is characteristic. Enlarged adnexa may be found if an endometrioma is present.

WBC and erythrocyte sedimentation rate (ESR) are normal. CA-125 may be elevated. Sonogram will show an endometrioma if present.

Diagnosis. Diagnosis of endometriosis is made by laparoscopy. There is a suspicion of the disease based on history and physical exam; however, laparoscopic identification of endometriotic nodules or endometriomas is definitive.

Management seeks to prevent shedding of the ectopic endometrial tissue, thus decreasing adhesion formation and pain.

- **Pregnancy** can be helpful to endometriosis because during this time there is no menstruation; also, the dominant hormone throughout pregnancy is progesterone, which causes atrophic changes in the endometrium. However, infertility may make this impossible.
- **Pseudopregnancy** achieves this goal through preventing progesterone withdrawal bleeding. Continuous oral medroxyprogesterone acetate (MPA [Provera]), subcutaneous medroxyprogesterone acetate (SQ-DMPA [Depo-Provera]), or combination oral contraceptive pills (OCPs) can mimic the atrophic changes of pregnancy.
- **Pseudomenopause** achieves this goal by making the ectopic endometrium atrophic. The treatment is based on inhibition of the hypothalamic–pituitary–ovarian axis to decrease the estrogen stimulation of the ectopic endometrium. Testosterone derivative (danazol) and gonadotropin-releasing hormone (GnRH) analog (leuprolide) can be used to achieve inhibition of the axis.

The best inhibition of the hypothalamic–pituitary–ovarian axis is achieved by GnRH analogs. GnRH stimulates the pituitary in a pulsatile fashion, and GnRH analogs stimulate by continuous stimulation, which produces a condition known as down-regulation of the pituitary.

Although regression of the endometriotic nodules can be achieved, the patient can become symptomatic with menopausal complaints. Patients on leuprolide therapy for >3–6 months can complain of menopausal symptoms such as hot flashes, sweats, vaginal dryness, and personality changes. Leuprolide is continued for 3–6 months and then a more acceptable medication for the inhibition of the axis can be used, e.g., birth control pill medication. An alternative to leuprolide is depot medroxyprogesterone acetate (DMPA), which also suppresses FSH and LH but does not result in vasomotor symptoms.

Surgical management can be conservative or aggressive.

- **Conservative.** If preservation of fertility is desired, the procedures can be performed in many cases through laparoscopic approach. Lysis of paratubal adhesions may allow adherent fimbria to function and achieve pregnancy. Ovarian cystectomies as well as oophorectomies can be treatment for endometriomas. Laser vaporization of visible lesions is also performed laparoscopically.
- **Aggressive.** If fertility is not desired, particularly if severe pain is present because of diffuse adhesions, definitive surgical therapy may be carried out through a total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO). Estrogen replacement therapy is then necessary.

Endometriosis is not a malignant condition, but is associated with higher risk of ovarian carcinoma; mechanism unclear.

Adenomyosis

Refer to Chapter 4, Disorders of the Cervix and Uterus.

Ectopic Pregnancy

Refer to Obstetrics, Chapter 2, Failed Pregnancy.

Fertility Control 9

Learning Objective

- List the advantages and disadvantages of different forms of contraception including barrier-spermicidal methods, steroid contraception, intrauterine contraception, coitus interruptus, natural family planning, lactation, vaginal douche, and sterilization

FERTILITY CONTROL

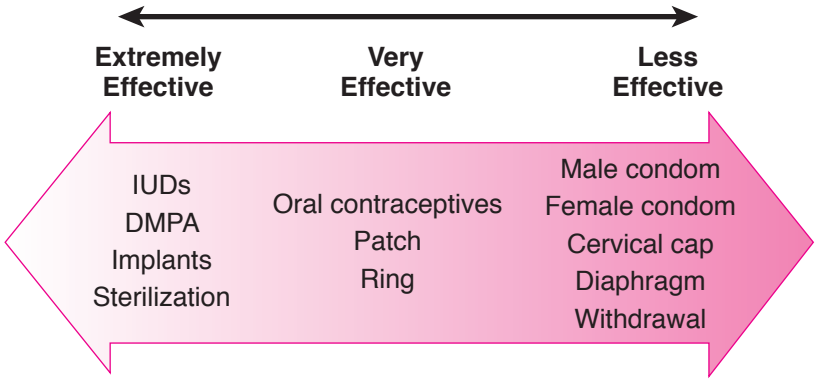


Figure II-9-1. Contraception

BARRIER-SPERMICIDAL METHODS

A 16-year-old adolescent comes to the family planning clinic requesting contraception. She has heard about the diaphragm and wonders if it would be appropriate for her.

Barrier-spermicidal methods of fertility control are locally active devices preventing entry of sperm in through the cervix, thus preventing pregnancy.

- **Advantages:** become increasingly effective with advancing age and the associated natural decline in fertility; protect against some STDs; have no systemic side effects
- **Disadvantages:** failure rate near 20%; are coitally dependent, requiring a decision for each use and thus decreasing spontaneity; have no impact on excessive menstrual flow or excessively painful menses

There are several types of barrier-spermicidal methods.

- **Condoms (most common):** penile sheaths that must be placed on the erect penis; no individual fitting is required
- **Vaginal diaphragm:** dome-shaped device placed in the anterior and posterior vaginal fornices holding spermicidal jelly against the cervix; can be placed an hour before intercourse; individual fitting is required (if too large a size is used, can result in urinary retention)
- **Spermicides:** active ingredient is nonoxynol-9, a surface-active agent that disrupts cell membranes (and thus may cause side effect of genital membrane irritation); can take the form of jellies or foams placed into the vagina

STEROID CONTRACEPTION

A 44-year-old woman, gravida 4 para 4, presents with questions about oral steroid contraception. She uses a diaphragm but is worried about contraceptive failure. She also expresses concern that her menses have become slightly heavier and more painful. She does not smoke and has no other medical problems.

Steroid contraception inhibits the midcycle luteinizing hormone (LH) surge, thus preventing ovulation; alters cervical mucus making it thick and viscid, thus retarding sperm penetration; and alters endometrium, thus inhibiting blastocyst implantation.

Table II-9-1. Mechanism of Action of Steroid Contraception

Pituitary	Suppressed LH surge
Ovary	Suppressed ovulation
Endometrium	Atrophy
Cervix	Hostile mucus

Estrogen-mediated metabolic effects include fluid retention from decreased sodium excretion, accelerated development of cholelithiasis, increase in hepatic protein production (e.g., coagulation factors, carrier proteins, angiotensinogen), healthy lipid profile changes (increased HDL, decreased LDL), and increased venous and arterial thrombosis.

Progestin-mediated metabolic effects include mood changes and depression from decreased serotonin levels, androgenic effects (e.g., weight gain, acne), and unhealthy lipid profile changes (decreased HDL, increased LDL).

Absolute contraindications include pregnancy, acute liver disease, history of vascular disease (e.g., thromboembolism, deep venous thrombosis [DVT], cerebrovascular accident [CVA], systemic lupus erythematosus [SLE]), hormonally dependent cancer (e.g., breast), smoker age $\geq$35, uncontrolled hypertension, migraines with aura, diabetes mellitus with vascular disease, and known thrombophilia.

Relative contraindications include migraine headaches, depression, diabetes mellitus, chronic hypertension, and hyperlipidemia.

Noncontraceptive benefits include decreased ovarian and endometrial cancer, decreased dysmenorrhea and dysfunctional uterine bleeding, and decreased PID and ectopic pregnancy.

Table II-9-2. Noncontraceptive Benefits of Steroid Contraception

Mostly Progestin Component
Decreased dysmenorrhea
Decreased dysfunctional uterine bleeding
Decreased pelvic inflammatory disease
Decreased ectopic pregnancy

Combination Modalities

Combination OCPs contain both an estrogen and a progestin. They are administered most commonly in one of two ways:

- Daily with 21 days on and 7 days off
- Daily with 24 days on and 4 days off

When one is "off" the hormones, withdrawal bleeding will occur. Failure rate is 2% with ideal use.

A newer combination is with daily hormones for 12 weeks followed by 1 week of placebo, which results in 4 periods a year rather than 13 with the traditional schedule.

Oral contraceptives: A unique combination of OCP (YAZ) reduces severe PMDD symptoms by 50%. It contains **ethinyl estradiol** and a new progestin, **drospirenone**. The dosing is 24 days of active pills then 4 days of placebo, rather than the traditional 21 days, followed by 7 days of placebo.

Combination vaginal ring, marketed under the trade name of NuvaRing, contains both an estrogen and a progestin. It is inserted into the vagina and then removed after 3 weeks for 1 week to allow for a withdrawal bleed. A major advantage is relatively stable and constant blood levels of hormones. Failure rate is similar to combination OCPs.

Transdermal skin patch, marketed under the trade name of Ortho Evra, contains both an estrogen and a progestin. A patch is replaced every week for 3 weeks then removed for 1 week to allow for a withdrawal bleed. Levels of steroids are 60% higher than combination OCPs.

Progestin-Only Modalities

Progestin-only OCPs contain only progestins and are sometimes called the "minipill." They need to be taken daily and continuously. A frequent side effect is breakthrough bleeding. Failure rate is 3% with ideal use.

Progestin-only injectable is an IM injection of **depo-medroxyprogesterone acetate** (DMPA) marketed under the trade name of Depo-Provera. The slow release allows administration only every 3 months. A frequent side effect is breakthrough bleeding. Other side effects are prolonged time for fertility return and decreased bone mineral density. Failure rate is <1%.

Progestin-only subcutaneous implant uses **etonogestrel** as the active ingredient and is marketed under the trade name of Nexplanon. The core contains a small amount of barium, making it visible on x-ray. The continuous release continues for 4 years. A frequent side effect is breakthrough bleeding. Failure rate is <1%.

Note

Of all the steroid contraceptives, combination OCPs are the only one to have regular, predictable menses.

"Morning-after" pill uses **levonorgestrel** tablets and is marketed under the trade name of "Plan B." This postcoital contraception is administered as one tablet, immediately followed by one additional tablet in 12 h. Failure rate is 1%.

General. A recent evaluation of women's views regarding contraceptive health benefits demonstrated that most women are unaware of the protective effects of OCPs against endometrial and ovarian cancer, PID, ectopic pregnancy, benign breast disease, anemia, and dysmenorrhea.

Risks and Benefits. In nonsmoking women age >40, currently available OCPs are extremely safe. Low-dose contraceptive pills do not significantly increase the risk of cancer, heart disease, or thromboembolic events in women with no associated risk factors (hypertension, diabetes, or smoking). The combination estrogen/progestin pill tends to reduce menstrual flow and dysmenorrhea and regulates the menses, all excellent benefits for the patient.

INTRAUTERINE CONTRACEPTION

> A 30-year-old woman with Crohn's disease who periodically requires steroid therapy seeks advice regarding long-term contraception. She has had 3 pregnancies. A subserosal, fundal fibroid was noted at the time of her previous cesarean section delivery. She states that she is in a mutually monogamous relationship. She was treated for a chlamydia infection 2 months ago but does not like the idea of hormonal contraception and is asking about the risks associated with an IUS.

Intrauterine system (IUS) contraception is a long-acting reversible contraceptive method that involves placement of a small T-shaped object inside the uterus. Failure rate is <1%. Continuation rates at 1 year are almost 80%.

Mechanisms of action include the following:

- Decreased sperm transport
- Increased tubal motility (causing failure of implantation of immature zygote)
- Decreased implantation secondary to endometrial inflammation
- Phagocytic destruction of sperm and blastocyst
- Alteration of cervical mucus (only progesterone IUSs)

Absolute contraindications include a confirmed or suspected pregnancy, known or suspected pelvic malignancy, undiagnosed vaginal bleeding, and known or suspected salpingitis. **Relative contraindications** include abnormal uterine size or shape, medical condition (e.g., corticosteroid therapy, valvular heart disease, or any instance of immune suppression increasing the risk of infection), nulligravidity, abnormal Pap smears, and history of ectopic pregnancy.

Side effects of IUS include increased menstrual bleeding and menstrual pain (with copper IUS but not progesterone IUS).

Potential complications include:

- **Expulsion** is higher in young, low parity women.
- **Ectopic pregnancy.** The IUS does not increase ectopic pregnancies. However, with pregnancy from failed IUS, the likelihood of it being ectopic is higher because primarily, intrauterine pregnancies are prevented.
- **Septic abortion** occurs in 50% of patients with concurrent pregnancy.

Note

The popularity of the IUS has varied greatly during the past 2 decades. Despite its excellence as a method of contraception, it has yet to recover from the negative publicity generated by the Dalkon Shield in the late 1970s. The LNG-containing IUS is effective for 5 years and the copper T-380A is effective for 10 years, making it potentially the **least expensive** contraceptive available.

- **Uterine perforation**, although rare, occurs more likely at time of insertion.
- **PID** may occur within the first 2 months after placement if pathogenic organisms are present in the reproductive tract.

Four types of IUD are available in the United States. Failure rate for all is <1%.

- Copper IUD: "**Paragard**" contains 380 mm^2 copper, approved for 10 years (abbrev TCu380A)
- Levonorgestrel (LNg) IUD: "**Mirena**" contains 52 mg LNg, approved for 5 years (abbrev LNg52/5)
- Levonorgestrel (LNg) IUD: "**Liletta**" contains 52 mg LNg, approved for 3 years (abbrev LNg52/3)
- Levonorgestrel (LNg) IUD: "**Skyla**" contains 13.5 mg LNg, approved for 3 years

LONG-ACTING REVERSIBLE CONTRACEPTION

Long-acting reversible contraceptives (LARCs) provide effective contraception for an extended period without requiring user action. Methods used include intramuscular injection (e.g. DMPA), IUD (Mirena, Paragard), and subdermal contraceptive implant (Nexplanon).

- **Advantages:** considered the most effective reversible method of contraception because patient compliance is not required; "typical use" failure rates (<1% per year) are about the same as "perfect use" failure rates (similar to sterilization procedures); long-lasting, convenient, well-liked by users, and very cost-effective
- **Disadvantages:** higher up-front cost ($800–900 in United States) as compared with other methods such as oral contraceptive pills, the patch, and vaginal ring

NATURAL FAMILY PLANNING—PERIODIC ABSTINENCE

This method is based on avoiding sexual intercourse around the time of predicted ovulation. It assumes the egg is fertilizable for 12–24 hours and sperm is capable of fertilizing the egg for 24–48 hours. It requires a high degree of discipline from both sexual partners. Methods include prediction or identification of ovulation inferred from menstrual records, basal body temperature charting (temperature rise from thermogenic effect of progesterone), and change in cervical mucus from thin and watery to thick and sticky (reflects the change from estrogen dominance preovulation to progesterone dominance postovulation).

- **Advantages:** inexpensive, readily available, no steroid hormonal side-effects, may be preferred for religious reasons
- **Disadvantages:** inaccurate prediction of ovulation, high failure rate because of human frailties and the passions of the moment

COITUS INTERRUPTUS

In this practice, also known as **withdrawal** or pull-out method, the man withdraws his penis from the woman's vagina prior to orgasm and ejaculation. It is one of the oldest contraceptive methods described.

- **Advantages:** readily available, inexpensive, free of systemic side effects
- **Disadvantages:** high failure rate, no protection against STDs, high degree of discipline required, semen can enter vagina and cervical mucus prior to ejaculation

VAGINAL DOUCHE

With vaginal douche, plain water, vinegar, and other products are used immediately after orgasm to theoretically flush semen out of the vagina. It has a long history of use in the United States.

- **Advantages:** none
- **Disadvantages:** high failure rate, no protection against STDs; sperm can enter the cervical mucus within 90 seconds of ejaculation

LACTATION

With lactation, elevated prolactin levels with exclusive breastfeeding inhibit pulsatile secretion of GnRH from the hypothalamus. Effectiveness is dependent on the frequency (at least every 4-6 hours day and night) and intensity (infant suckling rather than pumping) of milk removal.

- **Advantages:** enhanced maternal/infant health, bonding, and nutrition; readily available and inexpensive; needs no supplies; free of systemic side effects; acceptable to all religious groups
- **Disadvantages:** high failure rate if not exclusively breastfeeding; only reliable for up to six months, no protection against STDs

STERILIZATION

> A 38-year-old multipara has completed her childbearing and is requesting sterilization. All three of her children were delivered vaginally. She has no medical problems and is in good health. General and pelvic examination is unremarkable.

Sterilization is a surgical procedure usually involving ligation of the female oviduct or male vas deferens. After the procedure is performed, there is nothing to forget and nothing to remember. This method is considered permanent and irreversible.

- **Tubal ligation** (**most common** modality of pregnancy prevention in the United States). Destruction or removal of a segment of the oviduct is performed in an operating room through a transabdominal approach usually using a laparoscopy or minilaparotomy. Failure rate is 1 in 200; if the procedure fails and pregnancy results, an ectopic pregnancy should be ruled out.
- **Vasectomy:** Destruction or removal of a segment of vas deferens is performed as an outpatient procedure using local anesthesia. Failure rate is 1 in 500. A successful procedure can be confirmed by absence of sperm on a semen specimen obtained 12 ejaculations after the surgery. Sperm antibodies can be found in 50% of vasectomized patients.

Human Sexuality 10

Learning Objectives

- ❏ Take a sexual history
- ❏ Outline the human sexual response cycle
- ❏ List common sexual dysfunctions and their possible causes and treatments
- ❏ Explain the responsibilities of a health professional when examining a sexual assault victim

HUMAN SEXUAL RESPONSE CYCLE

A 31-year-old woman, mother of four children, comes to the office stating she has little interest in sexual intercourse with her husband for the past year. She says sex is painful, but she is able to experience orgasm occasionally. She has had no other sexual partners than her husband. These problems are affecting her marriage. She had a tubal sterilization procedure performed after her last delivery two years ago. Medications include thyroid replacement and fluoxetine.

Linear Model

Desire. In both women and men the desire for sexual activity is also known as libido. Desire is maintained by a balance between **dopamine** stimulation and **serotonin** inhibition. The threshold of response is determined by androgens, especially **testosterone**. This is true for women as well as men.

Excitement. This phase is also known as **arousal**. It is mediated by **parasympathetic** connections to the pelvic organs and results in vascular **engorgement**. Arousal in women is generally slower, responds more to **touch** and **psychic stimuli**, and is manifested by vaginal lubrication. Arousal in men is generally faster, responds more to **visual** stimuli, and is manifested by penile **erection**.

Plateau. This phase entails progression and intensification of the excitement phase. The length of this phase is variable. The neural pathway and physiologic mechanism are the same as excitement.

Orgasm. This phase is mediated by **sympathetic** connections resulting in reflex tonic-clonic **muscle contractions** of the pelvic floor followed by contractions of the uterus. Women have more individual orgasmic **variability** than men. A unique characteristic of women is the potential for consecutive **multiple orgasms**.

Resolution. This phase is marked by a return to basal physiologic state with reversal of vasocongestion and muscle tension. Resolution tends to be faster for men and slower for women.

Refractory Phase. This is a unique characteristic of men and is the period of inability to be aroused before another orgasm. It frequently varies directly with the age of the man.

Circular Relational Model

Masters and Johnson's **linear**, four-stage **biologic model of sexual response** for both men and women assumes that men and women have similar sexual responses. Many women, however, do not move progressively and sequentially through the phases as described. Women may not even experience all of the phases—for example, they may move from sexual arousal to orgasm and satisfaction without experiencing sexual desire, or they can experience desire, arousal, and satisfaction but not orgasm.

The biologic model **may be limited** because it does not take into account nonbiologic experiences such as pleasure and satisfaction. It also does not place sexuality into the context of the relationship.

Much of female sexual desire is actually a reaction to a partner's sexual interest rather than a spontaneous stirring of the woman's own libido. Women have many reasons for engaging in sexual activity other than sexual hunger or drive, as the traditional model suggests.

The **circular,** variable-stage **relationship model of female sexual response** acknowledges how emotional intimacy, sexual stimuli, and relationship satisfaction affect the female sexual response.

- Female sexual functioning proceeds in a more complex and circuitous manner than does male sexual functioning. Also, female functioning is dramatically and significantly affected by numerous psychosocial issues.
- Many women start from a point of sexual neutrality—where a woman is receptive to being sexual but does not initiate sexual activity—and the desire for intimacy prompts her to seek ways to become sexually aroused via conversation, music, reading or viewing erotic materials, or direct stimulation. Once she is aroused, sexual desire emerges and motivates.
- The goal of sexual activity for women is not necessarily orgasm, but rather personal satisfaction, which may be orgasm and/or feelings of intimacy and connection.

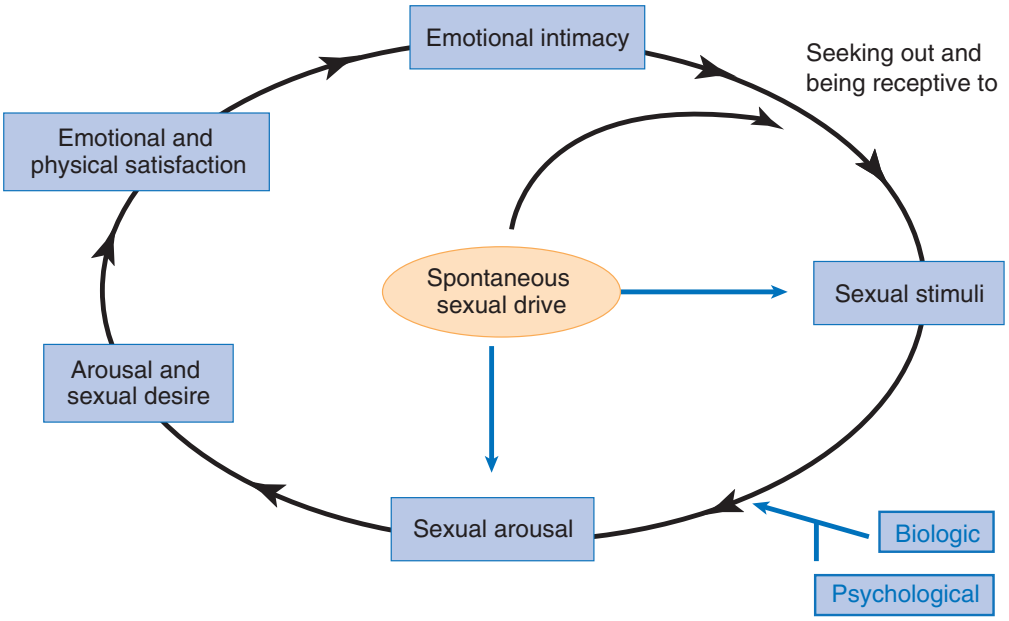


Figure II-10-1. Non-linear Model of Female Sexual Response

Non-linear model acknowledges how emotional intimacy, sexual stimuli, and relationship satisfaction affect female sexual response.

SEXUAL HISTORY-TAKING

The following questions should be asked of all new patients in developing a medical database and problem list.

- **Sexual activity.** Start out with the following initial question: Is the patient currently sexually active? If not now, has she been in past?
- **Current history.** If she is currently sexually active, ask the following: Is the relationship with men or women or both? Is the relationship satisfying? Does she have any difficulty lubricating? Does she have pain with intercourse?
- **Previous history.** What was her age at first intercourse? What is the number of lifetime and current sexual partners? Does she have a history of sexual abuse or rape?

SEXUAL DYSFUNCTION

Each phase of the sexual response cycle can be dysfunctional.

- **Desire disorders.** Decreased sexual desire is the most common female sexual complaint. It may be organic (e.g., low androgens), medication related (e.g., selective serotonin reuptake inhibitors [SSRIs]), or psychological (e.g., poor partner relationship). **Treatment** can be difficult if it is relational in etiology. **Flibanserin** (Addyi), a serotonin 5-HT receptor agonist, is approved for premenopausal women with hypoactive sexual desire disorder that causes distress.
- **Excitement disorders.** This usually results in difficulty in vaginal lubrication. The most common cause is estrogen deficiency. **Treatment** is highly successful.

- **Anorgasmia.** This can be primary or secondary. Inadequate clitoral stimulation is the most common cause. **Treatment** is highly successful using initially self-stimulation then partner education.
- **Dyspareunia.** Since pain with intercourse may arise from both psychological or physical causes, a thorough history and physical examination is essential. **Treatment** is directed at the specific cause found.
- **Vaginismus.** This occurs with painful reflex spasm of the paravaginal thigh adductor muscles. It is the only sexual dysfunction that can be diagnosed on physical examination. **Treatment** is highly successful using vaginal dilators.

SEXUAL ASSAULT

A 21-year-old university student presents to the emergency department stating she was walking home after an evening class when she was assaulted by a male stranger and was raped. She is not crying or upset, but rather looks almost without emotions. She is accompanied by her female roommate.

Definition. Rape is defined as sexual activity without the individual's consent occurring under coercion.

Management.

- **Stabilization.** The first step is to determine the patient's vital signs and take whatever is needed to stabilize them. An informed consent needs to be obtained.
- **History-taking.** Record the events that happened in the patient's own words. Also obtain a reproductive, obstetric, sexual, and contraceptive history.
- **Examination.** A thorough general and pelvic examination should be performed with photographic or drawing documentation of any injuries or trauma.
- **Specimens.** A rape kit should be used to obtain biologic specimens (e.g., vaginal, oral, or anal specimens) for DNA or other evidence for use in potential legal proceedings. These must be appropriately labeled and documented, including signatures of receiving authorities. Also obtain baseline laboratory tests: VDRL, HIV screen, pregnancy test, urine drug screen, and blood alcohol level.
- **Prophylaxis.** Antibiotic therapy should be administered prophylactically for gonorrhea (ceftriaxone 125 mg IM × 1), chlamydia (azithromycin 1 g PO × 1), and trichomoniasis (metronidazole 2 g PO × 1). Antiviral HIV prophylaxis should be administered within 24 hours after exposure, but no medication should be given after 36 hours. Active and passive immunization for hepatitis B is appropriate.
- **Pregnancy prevention.** Administer two tablets of high progestin OCPs immediately, repeating two tablets in 12 h. A newly released formulation of levonorgestrel tablets (Plan B) is available specifically for postcoital pregnancy prevention.

Menstrual Abnormalities 11

Learning Objectives

- ❑ Describe the menstrual cycle
- ❑ Give a differential diagnosis and management of disorders of the menstrual cycle, including premenarchal menstrual bleeding, abnormal vaginal bleeding, and primary/secondary amenorrhea

MENSTRUAL PHYSIOLOGY

The menstrual cycle is the cyclic pattern of activity of hypothalamus, pituitary, ovary, and uterus that produces a rhythm of bleeding every month for 30 years or more during the active reproductive phase of a woman's life.

Menarche is the first flow that signifies potential reproductivity. **Menopause** is the termination of the menstrual flow, which signifies diminished ovarian function.

Menstrual cycle occurs with the maturation of the hypothalamic–pituitary–ovarian axis. The hormones produced include gonadotropin-releasing hormone (GnRH) from the hypothalamus, which stimulates follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior pituitary, which stimulate estrogen and progesterone from the ovarian follicle.

Layers of the Endometrium

Functionalis zone is the superficial layer that undergoes cyclic changes during the menstrual cycle and is sloughed off during menstruation. It contains the spiral arterioles that undergo spasm with progesterone withdrawal.

Basalis zone is the deeper layer that remains relatively unchanged during the menstrual cycle and contains stem cells that function to renew the functionalis. It contains the basal arteries.

Phases of the Endometrium

Menstrual phase is defined as the first four days of the menstrual cycle, with the first day of menses taken as day 1. It is characterized by disintegration of the endometrial glands and stroma, leukocyte infiltration, and red blood cell (RBC) extravasation. Sloughing of the functionalis and compression of the basalis occurs.

Proliferative phase follows the menstrual phase and is characterized by endometrial growth secondary to estrogen stimulation, including division of stem cells that migrate through the stroma to form new epithelial lining of the endometrium and new endometrial glands. The length of the spiral arteries also increases. An **estrogen-dominant endometrium is unstable** and, in the presence of **prolonged anovulation**, will **undergo hyperplasia with irregular shedding over time**.

Secretory phase follows the proliferative phase and is characterized by glandular secretion of glycogen and mucus stimulated by progesterone from the corpus luteum. Endometrial stroma becomes edematous, and spiral arteries become convoluted. **A progesterone-dominant endometrium is stable** and will **not undergo irregular shedding**. Regression of the corpus luteum occurs by day 23 if there is no pregnancy, causing decreased levels of progesterone and estradiol and endometrial involution. Constriction of the spiral arteries occurs one day before menstruation, causing endometrial ischemia and release of prostaglandins, followed by leukocyte infiltration and RBC extravasation. The resulting necrosis leads to painful cramps and menstruation. When a pregnancy occurs, the serum β-human chorionic gonadotropin (β-hCG) becomes positive at day 22–23 of the cycle. The β-hCG becomes positive when the zygote implants into the endometrium, usually 7–8 days after ovulation. Therefore, the serum β-hCG becomes positive before the missed period.

Menstrual Cycle Hormones

FSH stimulates the growth of granulosa cells and induces the **aromatase** enzyme that converts androgens to estrogens. It raises the concentration of its own receptors on the granulosa cells. It stimulates the secretion of inhibin from the granulosa cells and is suppressed by inhibin.

LH stimulates the production of androgens by the theca cells, which then get converted to estrogens in the granulosa cells by the aromatase enzyme (two-cell theory). It raises the concentration of its own receptors in FSH-primed granulosa cells. The LH surge, which is dependent on a rapid rise in estrogen levels, stimulates synthesis of prostaglandins to enhance follicle rupture and ovulation. The LH surge also promotes luteinization of the granulosa cells in the dominant follicle, resulting in progesterone production as early as the 10th day of the cycle.

Estrogen is produced in the granulosa cells in response to even low FSH concentrations and stimulates proliferative changes in the endometrium. It has a negative feedback to FSH at the hypothalamic–pituitary level, but has a positive feedback to increase GnRH receptor concentrations. At low estrogen levels there is negative inhibitory feedback for LH release, but as the level of estradiol increase is sustained for 50 hours, there is a transition to a positive stimulatory feedback, leading to the LH surge.

Androgens include androstenedione and testosterone. They are precursors of estrogen and are produced in the theca cells. In lower concentrations they stimulate aromatase enzyme activity, whereas at high levels they inhibit it. Androgens inhibit FSH induction of LH receptors.

Progesterone is produced by the corpus luteum and stimulates secretory changes in the endometrium in preparation for blastocyst implantation.

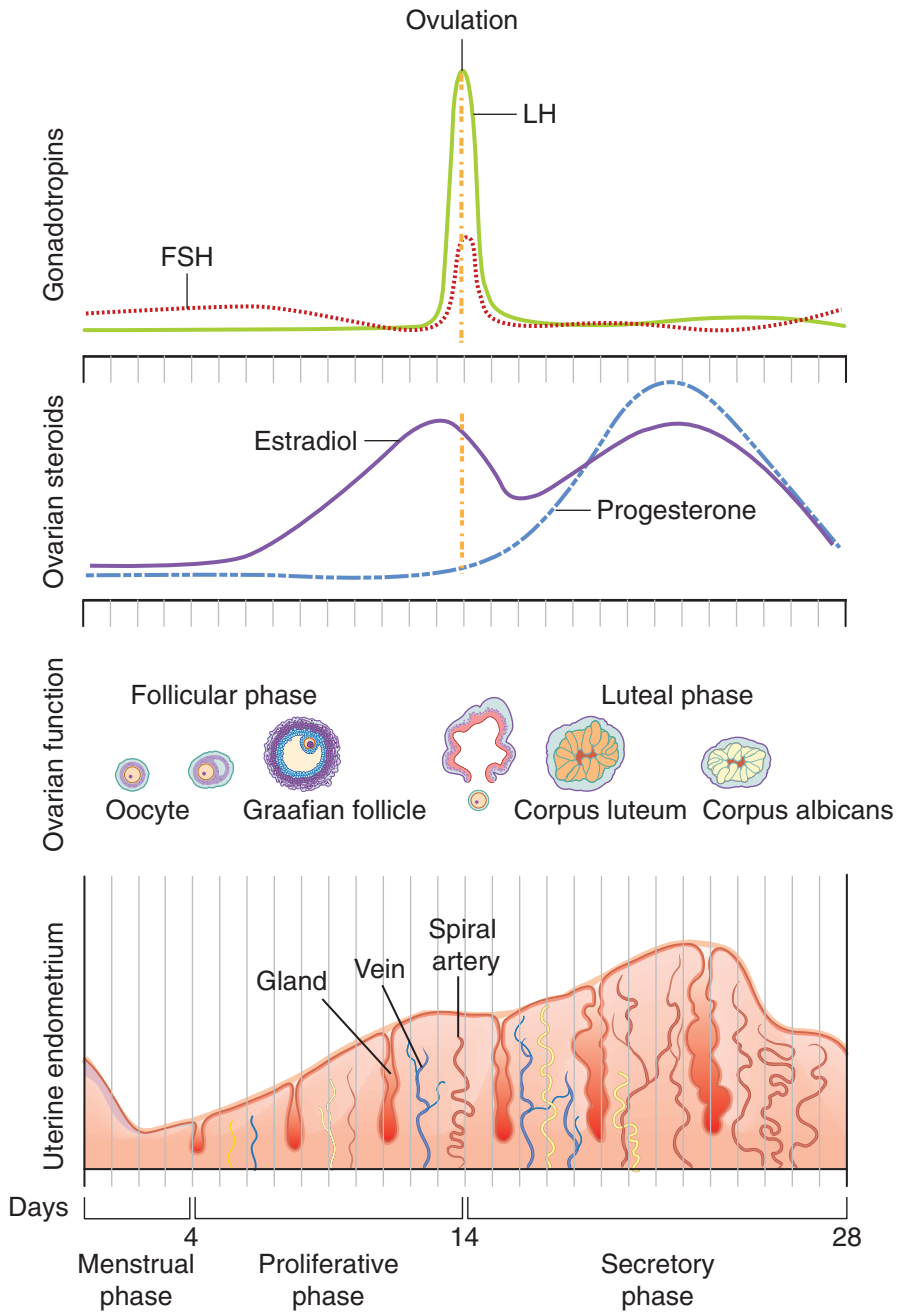


Figure II-11-1. Menstrual Cycle: Pituitary, Ovarian, and Endometrial Correlations

PREMENARCHAL VAGINAL BLEEDING

An 8-year-old girl is brought by her mother to the gynecologist's office because of vaginal bleeding for two weeks. The girl states that she has not taken any medication and gives no history suggestive of sexual abuse. She does not complain of headache or visual disturbance and has been doing well in school. On physical examination she is normal for her age without pubertal changes, and pelvic examination under sedation reveals a vaginal foreign body.

Premenarchal bleeding is bleeding that occurs before menarche (the average age at menarche is age 12). Possible causes include ingestion of estrogen medication, a foreign body that irritates the vaginal lining, a cancer of the vagina or of the cervix (sarcoma botryoides), a tumor of the pituitary or adrenal gland, an ovarian tumor, sexual abuse, or idiopathic precocious puberty. The most common cause of premenarchal bleeding is a foreign body.

Diagnosis and Management.

- **Pelvic examination.** The patient who complains of premenarchal bleeding should have a pelvic examination under sedation. In this examination, evidence of a foreign body, sexual abuse, or tumor is looked for. Sarcoma botryoides typically looks like grapes arising from the vaginal lining or from the cervix.
- **Imaging study.** CT scan or MRI scan of the pituitary, abdomen, and pelvis should be done. The scans are looking for evidence of a pituitary, ovarian, or adrenal tumor, which may cause early estrogen production.

ABNORMAL VAGINAL BLEEDING

A 31-year-old woman complains of six months of menometrorrhagia. The patient states that she started having menstruation at age 13 and that she has had regular menses until the past six months. The pelvic examination, including a Pap smear, is normal. She has no other significant personal or family history.

Pregnancy

In a patient who has abnormal bleeding during the reproductive age group, pregnancy or a complication must first be considered. Complications of early pregnancy that are associated with bleeding include incomplete abortion, threatened abortion, ectopic pregnancy, and hydatidiform mole.

Diagnosis. Urine or serum β-hCG test is required to confirm pregnancy. If pregnancy is identified vaginal ultrasound will help sort out which pregnancy complication is operative.

Management. Varies with the individual diagnosis.

Anatomic Lesion

If the pregnancy test is negative, then an anatomic cause of vaginal bleeding should be considered. The classic history is that of unpredictable bleeding (without cramping) occurring between normal, predictable menstrual periods (with cramping).

Various lower and upper reproductive tract factors can cause bleeding:

- Vaginal lesions: lacerations, varicosities, or tumors
- Cervical lesions: polyps, cervicitis, or tumors
- Endometrial lesions: submucous leiomyomas, polyps, hyperplasia, or cancer
- Myometrial lesions: adenomyosis

Diagnosis. A number of tests can be used to for anatomic diagnosis.

- Lower genital tract: pelvic and speculum exam
- Upper genital tract: saline sonogram, endometrial biopsy, or hysteroscopy

Management. Varies according to the individual diagnosis.

Inherited Coagulopathy

Up to 15% of patients with abnormal vaginal bleeding (especially in the adolescent age group) have coagulopathies. Review of systems may be positive for other bleeding symptoms including epistaxis, gingival bleeding, and ecchymoses. Von Willebrand disease is the most common hereditary coagulation abnormality. The three types can vary in severity.

Coagulopathies can be due to vessel wall disorders, platelet disorders, coagulation disorders, and fibrinolytic disorders. Von Willebrand disease arises from a deficiency of von Willebrand factor (vWF), a protein required for platelet adhesion.

Diagnosis. Positive family history and review of systems are helpful for screening. Initial lab tests include CBC with platelet count, PT, and PTT. The best screening test for Von Willebrand disease is a vWF antigen.

Management. Consultation with a hematology specialist for managing patients with inherited coagulopathies.

Dysfunctional Uterine Bleeding (DUB)

If the pregnancy test is negative, there are no anatomic causes for bleeding, and coagulopathy has been ruled out, then the diagnosis of hormonal imbalance should be considered. The classic history is that of bleeding which is unpredictable in amount, duration, and frequency (without cramping).

The most common cause of DUB is anovulation, which results in unopposed estrogen. With unopposed estrogen, there is continuous stimulation of the endometrium with no secretory phase.

An estrogen-dominant endometrium is structurally unstable as it increasingly thickens. With inadequate structural support, it eventually undergoes random, disorderly, and unpredictable breakdown resulting in estrogen breakthrough bleeding.

Diagnosis. Anovulatory cycles can usually be diagnosed from a history of irregular, unpredictable bleeding.

- Bleeding is usually without cramping since there is no PG release to cause myometrial contractions.
- Cervical mucus will be clear, thin, and watery, reflecting the estrogen dominant environment.
- Basal-body temperature (BBT) chart will not show a midcycle temperature rise due to the absence of the thermogenic effect of progesterone.
- Endometrial biopsy will show a proliferative endometrium.

GYN Triad

Endometrial Polyp or Submucosal Leiomyoma

- Predictable vaginal bleeding with intermenstrual bleeding
- 33-year-old woman
- Normal height and weight

GYN Triad

Abnormal Uterine Bleeding

PALM-COEIN Classification (FIGO 2011)

Visualizable by inspection or imaging:

P: Polyps (AUB-P)

A: Adenomyosis (AUB-A)

L: Leiomyoma (AUB-L)

M: Malignancy (AUB-M)

Needs further workup:

C: Coagulopathy (AUB-C)

O: Ovulatory disorders (AUB-O)

E: Endometrial (AUB-E)

I: Iatrogenic (AU B-1)

N: Not yet classified (AUB-N)

Progesterone trial involves administering progestin to stabilize the endometrium, stop the bleeding, and prevent random breakdown. When the progestin is stopped, spiral arteriolar spasm results in PG release, necrosis, and an orderly shedding of the endometrium.

- A positive progesterone trial confirms a clinical diagnosis of anovulation.
- A negative progesterone trial rules out anovulation.

Anovulation can be secondary to other medical conditions. It is important to identify and **correct a reversible cause of anovulation if present**.

- Hypothyroidism is a common cause of anovulation, diagnosed by a high TSH and treated with thyroid replacement.
- In hyperprolactinemia, diagnosed by a serum prolactin test, an elevated prolactin inhibits GnRH by increasing dopamine. Treatment depends on the cause of the elevated prolactin.

Progestin Management. Replacement of the hormone that is lacking (progesterone or progestin). These methods help regulate the menstrual flow and prevent endometrial hyperplasia, but do not reestablish normal ovulation.

- Cyclic MPA. Medroxyprogesterone acetate can be administered for the last 7–10 days of each cycle.
- Oral contraceptive pills (OCs). Estrogen-progestin oral contraceptives are often used for convenience. The important ingredient, however, is the progestin—not the estrogen.
- Progestin intrauterine system (LNG-IUS). The levonorgestrel IUS (Mirena or Skyla) delivers the progestin directly to the endometrium. This treatment can significantly decreasing menstrual blood loss.

Other Managements. If progestin management is not successful at controlling blood loss, the following generic methods have been successful:

- **NSAIDs** can decrease dysmenorrhea, improve clotting, and reduce menstrual blood loss. They are administered for only five days of the cycle and can be used and can be combined with OCs.
- **Tranexamic acid** (Lysteda) works by inhibiting fibrinolysis by plasmin. It is contraindicated with history of DVT, PE, or CVA, and not recommended with E+P steroids.
- **Endometrial ablation** procedure destroys the endometrium by heat, cold, or microwaves. It leads to an iatrogenic Asherman syndrome and minimal or no menstrual blood loss. Fertility will be affected.
- **Hysterectomy** (removal of the uterus) is a last resort and performed only after all other therapies have been unsuccessful.

PRIMARY AMENORRHEA

A 16-year-old girl presents with her mother, complaining she has never had a menstrual period. All of her friends have menstruated, and the mother is concerned about her daughter's lack of menstruation. On examination she seems to be well-nourished, with adult breast development and pubic hair present. Pelvic examination reveals a rudimentary vagina. No uterus is palpable on rectal examination.

Amenorrhea means an absence of menstrual bleeding. *Primary* means that menstrual bleeding has never occurred. Primary amenorrhea is diagnosed with an absence of menses at age 14 **without** secondary sexual development or at age 16 **with** secondary sexual development.

The origins of primary amenorrhea can be multiple; the two main categories are anatomic (e.g., vaginal agenesis/septum, imperforate hymen, or Müllerian agenesis) and hormonal (e.g., complete androgen insensitivity, gonadal dysgenesis [Turner syndrome], or hypothalamic-pituitary insufficiency).

Clinical Approach—Preliminary Evaluation.

- **Are breasts present or absent?** A physical examination will evaluate secondary sexual characteristics (breast development, axillary and pubic hair, growth). **Breasts are an endogenous assay of estrogen.** Presence of breasts indicates adequate estrogen production. Absence of breasts indicates inadequate estrogen exposure.
- **Is a uterus present or absent?** An ultrasound of the pelvis should be performed to assess presence of a normal uterus.

GYN Triad

Imperforate Hymen

- Primary amenorrhea
- (+) breasts and uterus
- Normal height and weight

Table II-11-1. Müllerian Agenesis versus Androgen Insensitivity

Breasts Present/ Uterus Absent	Müllerian Agenesis (46,XX)	Androgen Insensitivity (46,XY)
Uterus absent?	Idiopathic	MIF
Estrogen from?	Ovaries	Testes
Pubic hair?	Present	Absent
Testosterone level?	Female	Male
Treatment	No hormones Create vagina IVF—surrogate	Estrogen Create vagina Remove testes

Definition of abbreviations: MIF, Müllerian inhibitory factor.

Table II-11-2. Gonadal Dysgenesis versus HP Axis Failure

Breasts Absent/ Uterus Present	Gonadal Dysgenesis (45,X)	HP Axis Failure (46,XX)
FSH	↑	↓
Why no estrogen?	No ovarian follicles	Follicles not stimulated
Ovaries?	"Streak"	Normal
Treatment pregnancy	E + P Egg donor	E + P Induce ovulation (HMG)
Diagnostic test?	—	CNS imaging

Definition of abbreviations: E + P, estrogen and progestin; HMG, human menopausal gonadotropin.

GYN Triad

Müllerian Agenesis

- Primary amenorrhea
- (+) breasts but (–) uterus
- (+) pubic and axillary hair

GYN Triad

Androgen Insensitivity

- Primary amenorrhea
- (+) breasts but (–) uterus
- (–) pubic and axillary hair

GYN Triad

Gonadal Dysgenesis

- Primary amenorrhea
- (–) breasts but (+) uterus
- ↑ FSH levels

GYN Triad

Hypothalamic–Pituitary Failure

- Primary amenorrhea
- (–) breasts but (+) uterus
- ↓ FSH levels

Clinical Approach—Based on Findings Regarding Breasts and Uterus.

- **Breasts present, uterus present.** Differential diagnosis includes an imperforate hymen, vaginal septum, anorexia nervosa, excessive exercise, and possible pregnancy before first menses.
  - History and physical examination will identify the majority of specific diagnoses.
  - Otherwise the workup should proceed as if for secondary amenorrhea.
- **Breasts present, uterus absent.** Differential diagnosis is Müllerian agenesis (Mayer-Rokitansky-Kuster-Hauser syndrome) and complete androgen insensitivity (testicular feminization). Testosterone levels and karyotype help make the diagnosis.
  - **Müllerian agenesis.** These are genetically normal females (46,XX) with idiopathic absence of the Müllerian duct derivatives: fallopian tubes, uterus, cervix, and upper vagina; the lower vagina originates from the urogenital sinus.
    - Patients develop secondary sexual characteristics because ovarian function is intact; Müllerian ducts do not give rise to the ovaries.
    - Normal pubic and axillary hair is present. Testosterone levels are normal female.
    - **Management.** Surgical elongation of the vagina for satisfactory sexual intercourse.
  - **Androgen insensitivity.** In these genetically male (46,XY) individuals with complete lack of androgen receptor function, their bodies do not respond to the high levels of androgens present.
    - Without androgen stimulation, internal Wolffian duct structures atrophy. With testicular Müllerian inhibitory factor present, the Müllerian duct derivatives involute.
    - Without body recognition of dihydrotestosterone, external genitalia differentiate in a female direction. Patients function psychologically and physically as females and are brought up as girls. At puberty, when primary amenorrhea is noted, the diagnosis is made.
    - Female secondary sexual characteristics are present because the testes do secrete estrogens without competition from androgens. No pubic or axillary hair is noted. Testosterone levels are normal male.
    - **Management.** Testes removal at age 20 because the higher temperatures associated with the intra-abdominal position of the testes may lead to testicular cancer. Estrogen replacement is then needed.
- **Breasts absent, uterus present.** Differential diagnosis is gonadal dysgenesis (Turner syndrome) and hypothalamic–pituitary failure. FSH level and karyotype help make the diagnosis.
  - **Gonadal dysgenesis.** Turner syndrome (45,X) is caused by the lack of one X chromosome, essential for the presence of normal ovarian follicles. Instead of developing ovaries, patients develop streak gonads. FSH is elevated because of lack of estrogen feedback to the hypothalamus and pituitary. No secondary sexual characteristics are noted.
    - **Management.** Estrogen and progesterone replacement for development of the secondary sexual characteristics.

- **Hypothalamic–pituitary failure.** In the patient without secondary sexual characteristic but uterus present by ultrasound, another possibility is the hypothalamic causes of amenorrhea (stress, anxiety, anorexia nervosa, excessive exercise). FSH will be low. Kallmann syndrome is the inability of the hypothalamus to produce GnRH and also anosmia. The defect is in the area of the brain that produces GnRH, but it's also close to the olfactory center. CNS imaging will rule out a brain tumor.
- **Management.** Estrogen and progesterone replacement for development of the secondary sexual characteristics.

GYN Triad

Kallmann Syndrome

- Primary amenorrhea
- (–) breasts but (+) uterus
- Anosmia

SECONDARY AMENORRHEA

A 32-year-old woman states that her last menstrual period was one year ago. She started menses at age 12 and was irregular for the first couple of years, but since age 14 or 15 she has menstruated every 28–29 days. She has not been pregnant and is concerned about the amenorrhea. She has not been sexually active and has not used contraception. She has no other significant personal or family history. Physical examination, including a pelvic exam, is normal.

Amenorrhea means an absence of menstrual bleeding. *Secondary* means that menstrual bleeding had previously occurred. Secondary amenorrhea is diagnosed with absence of menses for three months **if previously regular menses** or six months **if previously irregular menses**.

There are multiple etiologies for secondary amenorrhea, which can be classified by alterations in FSH and LH levels. They include hypogonadotropic (suggesting hypothalamic or pituitary dysfunction), hypergonadotropic (suggesting ovarian follicular failure), and eugonadotropic (suggesting pregnancy, anovulation, or uterine or outflow tract pathology).

Specific Etiology.

- **Pregnancy.** The first step is a β-hCG to diagnose pregnancy. This is the most common cause of secondary amenorrhea.
- **Anovulation.** If no corpus luteum is present to produce progesterone, there can be no progesterone-withdrawal bleeding. Therefore, **anovulation** is associated with unopposed estrogen stimulation of the endometrium. Initially the anovulatory patient will demonstrate amenorrhea, but as endometrial hyperplasia develops, irregular, unpredictable bleeding will occur. The causes of anovulation are multiple, including PCOS, hypothyroidism, pituitary adenoma, elevated prolactin, and medications (e.g., antidepressants).
- **Estrogen Deficiency.** Without adequate estrogen priming the endometrium will be atrophic with no proliferative changes taking place. The causes of hypoestrogenic states are multiple, including absence of functional ovarian follicles or hypothalamic–pituitary insufficiency.
- **Outflow Tract Obstruction.** Even with adequate estrogen stimulation and progesterone withdrawal, menstrual flow will not occur if the endometrial cavity is obliterated or stenosis of the lower reproductive tract is present.

GYN Triad

Anovulatory Bleeding (Physiologic)

- Irregular, unpredictable vaginal bleeding
- 13-year-old adolescent
- Normal height and weight

GYN Triad

Anovulatory Bleeding (Chronic)

- Irregular, unpredictable vaginal bleeding
- 33-year-old woman
- Obese, hypertensive

Management.

- **Pregnancy Test.** The first step in management of secondary amenorrhea is to obtain a qualitative β-hCG test to rule out pregnancy.
- **Thyrotropin (TSH) Level.** If the β-hCG test is negative, hypothyroidism should be ruled out (TSH level). The elevated thyrotropin-releasing hormone (TRH) in primary hypothyroidism can lead to an elevated prolactin. If hypothyroidism is found, treatment is thyroid replacement with rapid restoration of menstruation.
- **Prolactin Level.**
  - **Medications.** An elevated prolactin level may be secondary to antipsychotic medications or antidepressants, which have an anti-dopamine side effect (it is known that the hypothalamic prolactin-inhibiting factor is dopamine).
  - **Tumor.** A pituitary tumor should be ruled out with CT scan or MRI of the brain. If a pituitary tumor is found and is <1 cm in its greatest dimension, treat medically with bromocriptine (Parlodel), a dopamine agonist. If >1 cm, treat surgically.
  - **Idiopathic.** If the cause of elevated prolactin is idiopathic, treatment is medical with bromocriptine.
- **Progesterone Challenge Test (PCT).** If the β-hCG is negative, and TSH and prolactin levels are normal, administer either a single IM dose of progesterone or seven days of oral medroxyprogesterone acetate (MPA).
  - **Positive PCT.** Any degree of withdrawal bleeding is **diagnostic of anovulation**. Cyclic MPA is required to prevent endometrial hyperplasia. Clomiphene ovulation induction will be required if pregnancy is desired.
  - **Negative PCT.** Absence of withdrawal bleeding is caused by either inadequate estrogen priming of the endometrium or outflow tract obstruction.
- **Estrogen–Progesterone Challenge Test (EPCT).** If the PCT is negative, administer 21 days of oral estrogen followed by 7 days of MPA.
  - **Positive EPCT.** Any degree of withdrawal bleeding is diagnostic of inadequate estrogen. An FSH level will help identify the etiology.
    - **Elevated FSH suggests ovarian failure.** If this occurs age <25, the cause could be Y chromosome mosaicism associated with malignancy, so order a karyotype. **Savage syndrome** or resistant ovary syndrome is a condition in which follicles are seen in the ovary by sonogram, though they do not respond to gonadotropins.
    - **Low FSH suggests hypothalamic–pituitary insufficiency.** Order a CNS imaging study to rule out a brain tumor. Whatever the result, women with a positive EPCT will need estrogen-replacement therapy to prevent osteoporosis and estrogen-deficiency morbidity. Cyclic progestins are also required to prevent endometrial hyperplasia.
  - **Negative EPCT.** Absence of withdrawal bleeding is diagnostic of either an outflow tract obstruction or endometrial scarring (e.g., **Asherman syndrome**). A hysterosalpingogram (HSG) will identify where the lesion is. Asherman is the result of extensive uterine curettage and infection-produced adhesions. It is treated by hysteroscopic adhesion lysis followed by estrogen stimulation of the endometrium. An inflatable stent is then placed into the uterine cavity to prevent re-adhesion of the uterine walls.

Hormonal Disorders 12

Learning Objectives

- ❑ Describe the causes of premenstrual disorders including precocious puberty
- ❑ Describe normal menopause and approaches to treating symptoms
- ❑ Outline the causes of hirsutism
- ❑ Provide epidemiology, diagnosis, and management information about polycystic ovarian syndrome
- ❑ List the steps for diagnosing infertility and treatment options available

PRECOCIOUS PUBERTY

A 6-year-old girl is brought to the office by her mother who has noticed breast budding and pubic hair development on her daughter. She has also experienced menstrual bleeding. Her childhood history is unremarkable until three months ago when these changes began.

The criteria for diagnosis of precocious puberty include development of female secondary sexual characteristics and accelerated growth before age 8 in girls and age 9 in boys. Precocious puberty is more common in girls than boys.

Normal Pubertal Landmarks. Complete puberty is characterized by the occurrence of all pubertal changes.

- The **most common initial change** is thelarche (breast development at age 9–10).
- This is followed by **adrenarche** (pubic and axillary hair at age 10–11).
- Maximal growth rate occurs at age 11 and 12.
- Finally, the last change is **menarche** (onset of menses at age 12–13).

Table II-12-1. Precocious Puberty

Diagnosis	Female secondary sexual characteristics Accelerated growth <8 years of age in girls	
Normal pubertal landmarks	Thelarche Breast development	9–10 years
	Adrenarche Pubic and axillary hair	10–11 years
	Maximal growth Growth spurt	11–12 years
	Menarche Onset of first menses	12–13 years

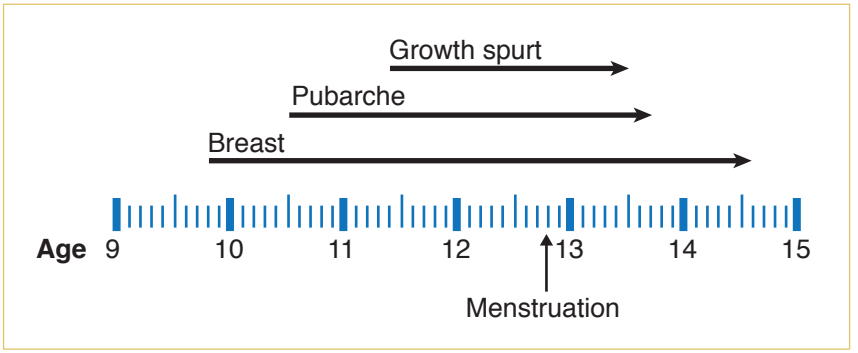


Figure II-12-1. Overview of Puberty

GYN Triad

Idiopathic or Constitutional

- Precocious complete isosexual puberty
- 6-year-old girl
- Normal head MRI

Incomplete Isosexual Precocious Puberty

Incomplete isosexual precocious puberty involves only *one* change: thelarche, adrenarche, or menarche. It is the result of either transient hormone elevation or unusual end-organ sensitivity. Management is conservative.

Complete Isosexual Precocious Puberty

Complete isosexual precocious puberty involves all changes of puberty, including breast development, growth spurt, and menstrual bleeding. The primary concern is premature closure of the distal epiphyses of the long bones, resulting in short stature. Fertility and sexual response are not impaired.

GYN Triad

CNS Lesions

- Precocious complete isosexual puberty
- 4-year-old girl
- Abnormal head MRI

- **Gonadotropin-dependent** occurs because of increased secretion of estrogens that are dependent on premature release of gonadotropins from the hypothalamus and pituitary.
  - **Idiopathic** (80% of cases): The **most common explanation** is constitutional without a pathologic process present. Patient typically age 6–7. The diagnosis is usually one of exclusion after CNS imaging is shown to be normal. **Management:** GnRH agonist suppression (leuprolide or Lupron) of gonadotropins until appropriate maturity or height has been reached.

  - **CNS pathology** (rare): A CNS pathologic process stimulates hypothalamic release of GnRH, which leads to FSH release and ovarian follicle stimulation of estrogen production. This may include hydrocephalus, von Recklinghausen disease, meningitis, sarcoid, and encephalitis. CNS imaging is abnormal. Patient typically age <6. **Management:** Directed at the specific pathologic process.

- **Gonadotropin-independent** occurs when estrogen production is independent of gonadotropin secretion from the hypothalamus and pituitary.
  - **McCune-Albright syndrome** (or polyostotic fibrous dysplasia) (5% of cases) is characterized by autonomous stimulation of aromatase enzyme production of estrogen by the ovaries. The syndrome includes multiple cystic bone lesions and **café au lait** skin spots. **Management:** Aromatase enzyme inhibitor.
  - **Granulosa cell tumor** (rare) is a gonadal-stromal cell ovarian tumor that autonomously produces estrogen. A **pelvic mass** will be identified on examination or pelvic imaging. **Management:** Surgical removal of the tumor.

Patients with idiopathic precocious puberty should be maintained with inhibition of the hypothalamic–pituitary–ovarian axis until the chronologic age catches up with the bone age.

Table II-12-2. Management of Precocious Puberty

Idiopathic	GnRH agonist
CNS lesions	Medical or surgical treatment
Ovarian tumor	Surgical excision
McCune-Albright	Aromatase inhibitors

GYN Triad

McCune-Albright Syndrome

- Precocious complete isosexual puberty
- 6-year-old girl
- Café-au-lait skin lesions

GYN Triad

Granulosa Cell Ovarian Tumor

- Precocious complete isosexual puberty
- 6-year-old girl
- Pelvic mass

PREMENSTRUAL DISORDERS

Premenstrual Syndrome

A 36-year-old patient complains of depression, anxiety, irritability, and breast tenderness, which occur on a monthly basis. On further questioning, the symptoms most commonly occur two weeks before her menstruation and disappear with menses.

Premenstrual syndrome (PMS) (5% of adult women) includes a wide range of physical and emotional difficulties, as well as the more severe affective changes included in premenstrual dysphoric disorder (PMDD). The basis for diagnosis is a **symptom diary** that the patient keeps throughout three menstrual cycles. The specific symptoms are less important than their temporal relationship to the menstrual cycle. All of the following must be present:

- Must be recurrent in at least three consecutive cycles
- Must be absent in the preovulatory phase of the menstrual cycle
- Must be present in the two postovulatory weeks
- Must interfere with normal functioning
- Must resolve with onset of menses

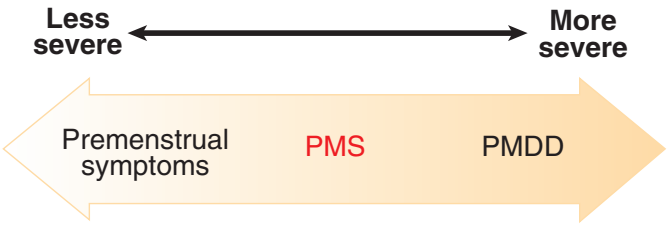


Figure II-12-2. Premenstrual Syndrome Diagnosis by Symptoms

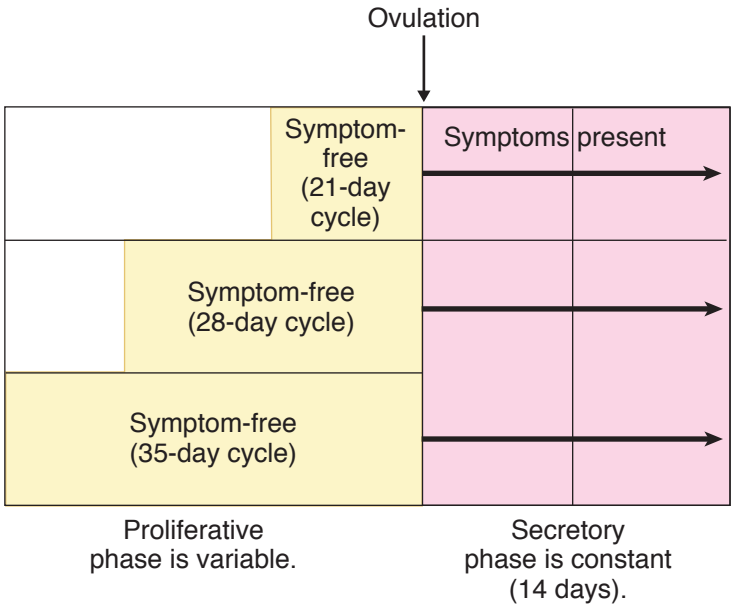


Figure II-12-3. Premenstrual Syndrome Diagnosis by Timing

Symptoms may vary, but they include fluid retention (bloating, edema, breast tenderness), autonomic changes (insomnia, fatigue, heart pounding), emotional symptoms (crying, anxiety, depression, mood swings), and musculoskeletal complaints (headache, muscle aches, joint aches). The most common affective symptom is **mood swings**, and the most common physical symptom is **abdominal bloating**.

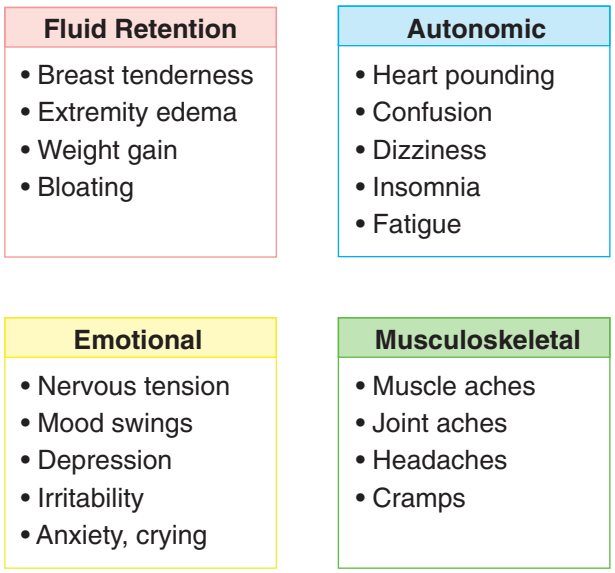


Figure II-12-4. PMS Symptoms

Management. **Proven treatments** include the following:

- **Selective serotonin reuptake inhibitors (SSRIs).** Fluoxetine hydrochloride, natural progesterone vaginal suppositories, medroxyprogesterone acetate, spironolactone, and vitamin B6 (pyridoxine). All of these options have been proposed for the treatment of PMS, but only fluoxetine, alprazolam, and GnRH agonists have been shown in controlled, double-blind trials to be superior to placebo for the more severe symptoms of PDD. Recently reported double-blind trials of fluoxetine have shown reductions of 40–75% in troublesome behavioral and emotional symptoms. Similar outcomes have been reported for buspirone hydrochloride and meclofenamate sodium in descriptive studies. SSRIs are the **treatment of choice** for emotional symptoms of PMS.
- **Drospirenone/ethinyl estradiol** (Yaz), with the unique progestin drospirenone (DRSP), has been approved by the FDA for the treatment of PMS. It is a low-dose, monophasic combination oral contraceptive with 24 hormone days and only a four-day hormone-free interval. Studies show that PMS symptoms are decreased with a shorter hormone-free time period. DRSP is an analogue of spironolactone, which differs from other OCP progestins by exhibiting both antimineralocorticoid and antiandrogenic effects.

Unproven treatments include the following:

- **Progesterone therapy** has a long history in the treatment of PMS, but neither natural progesterone (vaginal suppositories) nor progestin therapy has been shown to be any more effective than placebo. Because of both a lack of efficacy and the possibility of inducing menstrual irregularities, these agents should not be used.
- **Diuretics.** Because of the common complaint of "bloating" voiced by many patients with PMS, diuretics such as spironolactone have been advocated. Spironolactone has been studied in double-blind, randomized trials, and the results have been mixed. Although spironolactone may relieve some symptoms for some patients, the lack of consistent response across the studies in the literature suggests that other therapy is more effective.

- **Pyridoxine.** Vitamin B6 in doses of 50–200 mg/d has been suggested as a treatment for PMS. A number of randomized, blinded studies have been performed, but no conclusive findings have emerged. Because of the lack of demonstrated efficacy and the possibility of permanent sensory neuropathy associated with high-dose vitamin B6 consumptions, the use of vitamin B6 should be discouraged.

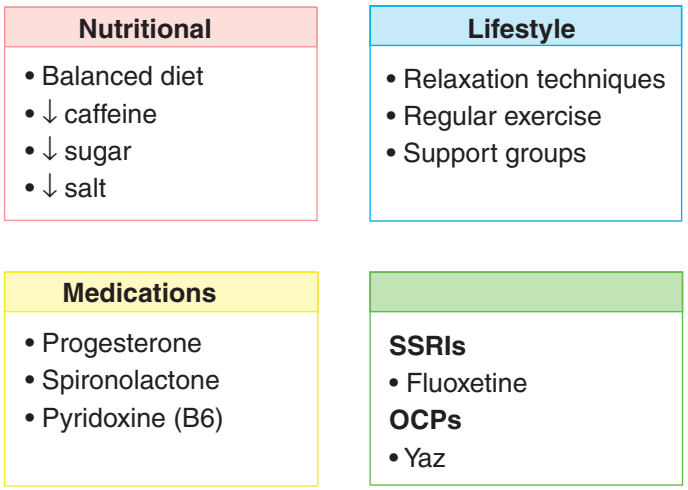


Figure II-12-5. PMS Treatment

HIRSUTISM

A 28-year-old woman complains of increased hair growth on the face and on the chest. She states that this has been going on for the past 10 years; however, she is more conscious of it at the present time. Her menses are irregular and unpredictable. Even though she has been married for 8 years and never used contraception, she has never been pregnant. On pelvic examination the ovaries bilaterally are slightly enlarged but no other abnormalities are noted.

Note

Virilization is excessive male-pattern hair growth in a woman **plus other masculinizing signs** such as clitoromegaly, baldness, lowering of voice, increasing muscle mass, and loss of female body contours.

Hirsutism (5–10% of adult women) is excessive male-pattern hair growth in a woman on the upper lip, chin, chest, abdomen, back, and proximal extremities. It involves the conversion of **vellus hair** (fine, nonpigmented hair) to **terminal hair** (coarse, dark hair) within the hair follicle. This conversion is under the influence of androgens.

In women, androgens are generally produced in only three body locations: the ovaries, the adrenal glands, and within the hair follicle. The workup of hirsutism will seek to identify which of these body locations is producing the androgens that are responsible for the excess terminal hair.

Clinical Approach.

- **History.** Is there a positive family history? What was the age of onset? Was onset gradual or abrupt? Have menstrual periods been irregular or regular? Is medication history positive for androgenic steroids?
- **Examination.** What is body-mass index? Location of excess hair? Evidence of virilization (frontal balding, loss of female body contour, clitoromegaly)? Presence of adnexal masses?

Lab tests will help to identify the elevated free androgens.

- **Dehydroepiandrosterone sulfate (DHEAS)** is produced only in the adrenal glands. A markedly elevated DHEAS is consistent with an adrenal tumor.
- **17-OH progesterone** is a precursor in the biosynthesis pathway of cortisol. It is elevated in late-onset congenital adrenal hyperplasia (CAH), with 21-hydroxylase deficiency. It is converted peripherally into androgens.
- **Testosterone** is produced by both the ovary and the adrenal glands. A mildly elevated level is suggestive of polycystic ovarian syndrome (PCOS). A markedly elevated level is consistent with an ovarian tumor.

Clinical Entities

Adrenal tumor: typically the onset has been **rapid** without positive family history.

- **Examination.** Physical examination will show evidence of **virilization**. Pelvic examination is unremarkable.
- **Laboratory tests.** DHEAS level is markedly elevated.
- **Imaging.** CT or MRI scan will show an abdominal-flank mass.
- **Management.** Surgical removal of tumor.

Ovarian tumor: typically the onset has been **rapid** without positive family history.

- **Examination.** Physical examination will show evidence of **virilization**. An adnexal mass will be palpated on pelvic examination.
- **Laboratory tests.** Testosterone level is markedly elevated.
- **Imaging.** Pelvic U/S will show an adnexal mass.
- **Management.** Surgical removal of the mass, usually a Sertoli-Leydig or hilus cell tumor.

Congenital adrenal hyperplasia (21-hydroxylase deficiency): typically the onset has been **gradual** in the second or early third decade of life and is associated with menstrual irregularities and anovulation. Precocious puberty with short stature is common. Family history may be positive. Late-onset CAH is one of the most common autosomal recessive genetic disorders.

- **Examination.** Physical examination will show evidence of **hirsutism** without virilization. Pelvic examination is unremarkable.
- **Laboratory tests.** Serum 17-OH progesterone level is markedly elevated.
- **Management.** Continuous corticosteroid replacement to arrest the signs of androgenicity and restore ovulatory cycles.

GYN Triad

Adrenal Tumor

- Abrupt-onset virilization
- Abdominal/flank mass
- ↑↑ DHEAS levels

GYN Triad

Ovarian Tumor (Sertoli-Leydig)

- Abrupt-onset virilization
- Pelvic mass
- ↑↑ testosterone levels

GYN Triad

Congenital Adrenal Hyperplasia 21-OH Deficiency

- Gradual-onset hirsutism
- Normal exam
- ↑ 17-OH progesterone

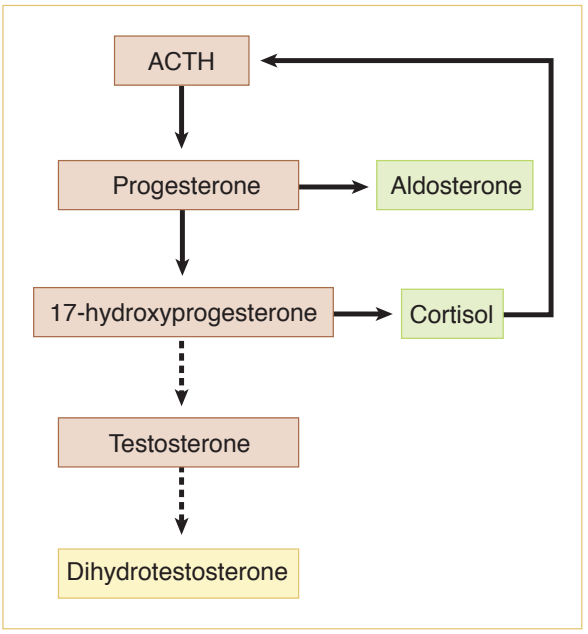


Figure II-12-6. Normal Adrenal Function

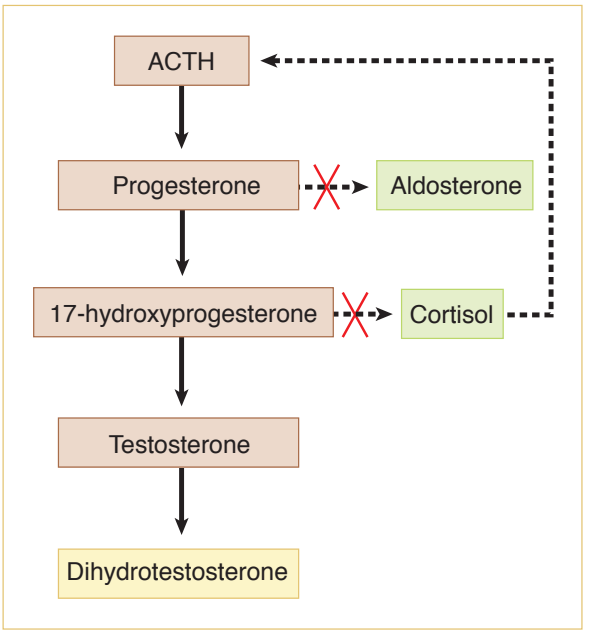


Figure II-12-7. Adrenal Hyperplasia

Polycystic Ovarian Syndrome (PCOS): typically the onset has been **gradual**, frequently with a positive family history. In addition, the history is positive for irregular bleeding and infertility.

- **Examination.** Physical examination usually reveals **hirsutism**, often with obesity and increased acne. Bilaterally enlarged, smooth, mobile ovaries will be palpated on pelvic examination. **Acanthosis nigricans** may be seen.
- **Laboratory tests.** Testosterone level is mildly elevated. LH to FSH ratio is elevated (3:1). Sex hormone binding globulin (SHBG) is decreased.
- **Imaging.** Pelvic U/S will show bilaterally enlarged ovaries with multiple subcapsular small follicles and increased stromal echogenicity.
- **Management.** Combination OCPs, which will lower free testosterone levels in two ways: by suppressing LH stimulation of the ovarian follicle theca cells and by increasing SHBG (thus decreasing free testosterone). Metformin can decrease insulin resistance and lower testosterone levels.

Idiopathic: typically the onset has been **gradual**, frequently with a positive family history. Menses and fertility are normal. This is the **most common** cause of androgen excess in women.

- **Examination.** Physical examination reveals **hirsutism** without virilization. Pelvic examination is normal.
- **Laboratory tests.** Normal levels of testosterone, DHEAS, and 17-OH progesterone are identified.
- **Management. Spironolactone**, a potassium-sparing diuretic whose mechanism of action as an antiandrogen is twofold: it is an androgen-receptor blocker and it also suppresses hair follicle 5-α reductase enzyme conversion of androstenedione and testosterone to the more potent dihydrotestosterone. **Eflornithine** is the first topical drug for the treatment of unwanted facial and chin hair. It blocks ornithine decarboxylase (ODC), which slows the growth and differentiation of the cells within the hair follicles.

GYN Triad

Idiopathic (Hair Follicle)
↑ 5-α Reductase Activity

- Gradual-onset hirsutism
- Normal exam
- Normal DHEAS, testosterone, 17-OH progesterone

POLYCYSTIC OVARIAN SYNDROME

A 32-year-old woman visits the gynecologist's office complaining of vaginal bleeding, facial hair growth, and obesity. She states that she has noted the facial hair growth for many years and the irregular bleeding has been progressively getting worse during the past six months. She has no other significant personal or family history, and on pelvic examination she has slightly enlarged bilateral ovaries. A rectovaginal examination is confirmatory.

Polycystic ovarian syndrome (PCOS), historically called Stein-Leventhal syndrome, is a condition of chronic anovulation with resultant infertility. The patient presents typically with irregular vaginal bleeding. Other symptoms include obesity and hirsutism.

- **Chronic anovulation.** Instead of showing the characteristic hormone fluctuation of the normal menstrual cycle, PCOS gonadotropins and sex steroids are in a steady state, resulting in anovulation and **infertility**. Without ovulation, there is no corpus luteum to produce progesterone. Without progesterone, there is unopposed estrogen. Endometrium, which is chronically stimulated by estrogen, without progesterone ripening and cyclic shedding becomes hyperplastic with **irregular bleeding**. With time **endometrial hyperplasia** can result, which could progress to endometrial cancer.
- **Increased testosterone.** Increased LH levels cause increased ovarian follicular theca cell production of androgens. The increased levels of androstenedione and testosterone suppress hepatic production of SHBG by 50%. The combined effect of increased total testosterone and decreased SHBG leads to mildly elevated levels of free testosterone. This results in **hirsutism**. PCOS is one of the **most common** causes of hirsutism in women.
- **Ovarian enlargement.** On ultrasound the ovaries demonstrate the presence of the necklace-like pattern of multiple peripheral cysts (20–100 cystic follicles in each ovary). The increased androgens prevent normal follicular development, inducing premature follicle atresia. These multiple follicles, in various stages of development and atresia, along with stromal hyperplasia and a thickened ovarian capsule result in ovaries that are bilaterally enlarged.

Table II-12-3. "HA-IR-AN" Syndrome (Polycystic Ovarian Syndrome)

HA	**H**yper**A**ndrogenism
IR	**I**nsulin **R**esistance
AN	**A**canthosis **N**igricans

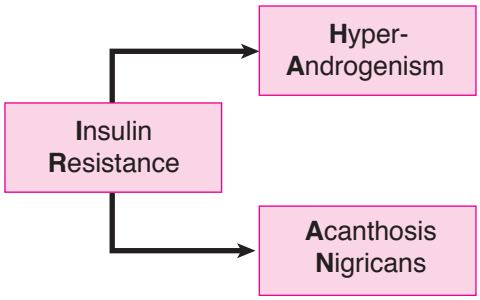


Figure II-12-8. Polycystic Ovarian Syndrome

Diagnosis is based on the Rotterdam criteria, which requires two of the following three findings:

- **Oligomenorrhea** or menstrual dysfunction
- **Hyperandrogenism**, clinically or biochemically
- **Polycystic ovaries** on TV sonogram (≥12 peripheral cysts)

Management. Directed toward the primary problem and the patient's desires.

- With **irregular bleeding**, OCPs will normalize the bleeding. The progestin component will prevent endometrial hyperplasia.
- **Hirsutism** can be suppressed two ways: OCPs will (a) lower testosterone production by suppressing LH stimulation of the ovarian follicle theca cells, and (b) increase SHBG (thus decreasing free testosterone). Spironolactone suppresses hair follicle 5-α reductase enzyme conversion of androstenedione and testosterone to the more potent dihydrotestosterone.
- **Infertility.** If patient desires pregnancy, ovulation induction can be achieved through clomiphene citrate or human menopausal gonadotropin. Metformin, a hypoglycemic agent that increases insulin sensitivity, can enhance the likelihood of ovulation both with and without clomiphene.

INFERTILITY

> A 30-year-old woman comes to the gynecologist's office complaining of infertility for one year. She and her husband have been trying to achieve pregnancy for more than a year and have been unsuccessful. There is no previous history of pelvic inflammatory disease and she used oral contraception medication for six years. Pelvic examination is normal, and a Pap smear is done.

Infertility (affected by 15% of couples in United States) is defined as the inability to achieve pregnancy with frequent and unprotected sexual intercourse for **12 months if woman age <35** or **6 months if woman age ≥35**. Both male and female factors have to be evaluated in the patient with infertility.

Fecundability is the likelihood of conception occurring with one cycle of appropriately timed mid-cycle intercourse. With the female partner age 20, the fecundity rate is 20%. By age 35, the rate drops to 10%.

Initial Noninvasive Tests

Semen analysis

- **Normal values.** Expected findings are volume >2 ml; pH 7.2–7.8; sperm density >20 million/ml; sperm motility >50%; and sperm morphology >50% normal. If values are abnormal, repeat the semen analysis in 4–6 weeks because semen quality varies with time.
- **Timing.** The first step in the infertility evaluation is a semen analysis, which should be obtained after 2–3 days of abstinence and examined within 2 h.

- **Minimally abnormal.** If sperm density is mild to moderately lower than normal, intrauterine insemination may be used. Washed sperm are directly injected into the uterine cavity. Idiopathic oligozoospermia is the most common male infertility factor.
- **Severely abnormal.** If semen analysis shows severe abnormalities, intracytoplasmic sperm injection may be used in conjunction with in vitro fertilization and embryo transfer.
- **No viable sperm.** With azoospermia or failed ICSI, artificial insemination by donor (AID) may be used.

Anovulation

Of all causes of infertility, treatment of anovulation results in the greatest success.

- **History.** Typically history is irregular, unpredictable menstrual bleeding, most often associated with minimal or no uterine cramping.
- **Objective data.** A basal body temperature (BBT) chart will not show the typical midcycle temperature elevation. A serum progesterone level will be low. An endometrial biopsy shows proliferative histology.
- **Correctible causes.** Hypothyroidism or hyperprolactinemia
- **Ovulation induction.** The agent of choice is **clomiphene** citrate administered orally for five days beginning on day five of the menstrual cycle. The biochemical structure of clomiphene is very similar to estrogen, and clomiphene fits into the estrogen receptors at the level of the pituitary. The pituitary does not interpret clomiphene as estrogen and perceives a low estrogen state, thus producing high levels of gonadotropins. **HMG** is administered parenterally and is used to induce ovulation if clomiphene fails. Careful monitoring of ovarian size is important because ovarian hyperstimulation is the **most common major side effect** of ovulation induction. When a patient is given clomiphene, her own pituitary is being stimulated to secrete her own gonadotropins, whereas when a patient is administered HMG, the patient is being stimulated by exogenous gonadotropins.

Follow-Up Invasive Tests

Hysterosalpingogram and laparoscopy

Tubal disease. Assessment of fallopian tube abnormalities is the next step if the semen analysis is normal and ovulation is confirmed.

- **Hysterosalpingogram (HSG).** In this imaging procedure, a catheter is placed inside the uterine cavity, and contrast material is injected. The contrast material should be seen on x-ray images spilling bilaterally into the peritoneal cavity. It should be scheduled during the week after the end of menses after prophylactic antibiotics to prevent causing a recurrent acute salpingitis. No further testing is performed if the HSG shows normal anatomy. If abnormal findings are seen, the extent and site of the pathology are noted and laparoscopy considered.
- **Chlamydia antibody.** A negative IgG Antibody test for chlamydia virtually rules out infection induced tubal adhesions.
- **Laparoscopy.** If potentially correctible tubal disease is suggested by the HSG, the next step in management is to visualize the oviducts and attempt reconstruction if possible (tuboplasty). If tubal damage is so severe surgical therapy is futile, then IVF should be planned.

Unexplained Infertility

A diagnosis of unexplained fertility is reserved for couples in which the semen analysis is normal, ovulation is confirmed, and patent oviducts are noted. Approximately 60% of patients with unexplained infertility will achieve a spontaneous pregnancy within the next three years.

Management. Controlled ovarian hyperstimulation (COH) with clomiphene, and appropriately timed preovulatory intrauterine insemination (IUI). The fecundity rates for six months are comparable with IVF with a significantly lower cost and risk.

With IVF, eggs are aspirated from the ovarian follicles using a transvaginal approach with the aid of an ultrasound. They are fertilized with sperm in the laboratory, resulting in the formation of embryos. Single embryo transfer is recommended for most patients to avoid iatrogenic high-order multiple pregnancy.

Ovarian Reserve Testing

Ovarian reserve testing (ORT) (mostly reserved for infertile women age ≥35) refers to assessment of the capacity of the ovary to provide eggs that are capable of fertilization. It is a function of (a) the number of follicles available for recruitment, and (b) the health and quality of the eggs in the ovaries.

The most significant factor affecting ORT is a woman's chronological age, with a major decrease around age 35. The ORT tests help predict whether a woman will respond to ovarian stimulation or whether it would be best to proceed directly to in vitro fertilization (IVF).

- **Day 3 FSH** level (**most commonly used**) is expected to be low due to the feedback of estrogen from the stimulated follicles. An increased FSH occurs if there is follicle depletion.
- **Anti-Müllerian hormone** (AMH): This glycoprotein is produced exclusively by small antral ovarian follicles and is therefore a direct measure of the follicular pool. As the number of ovarian follicles declines with age, AMH concentrations will decline.
- **Antral follicle count** (AFC) is the total number of follicles measuring 2–10 mm in diameter that is observed during an early follicular phase transvaginal sonogram. The number of AF correlates with the size of the remaining follicle pool retrieved by ovarian stimulation. AFC typically declines with age.

MENOPAUSE

A 53-year-old woman visits the gynecologist's office complaining of hot flashes, vaginal dryness, and irritability. She states that her symptoms started one year ago and have progressively been getting worse. Her last gynecologic examination was two years ago, at which time her mammogram was normal.

Menopause is a retrospective diagnosis and is defined as 12 months of amenorrhea. It is associated with the elevation of gonadotropins (FSH and LH). The mean age of 51 years is genetically determined and unaffected by pregnancies or use of steroid contraception. Smokers experience menopause up to two years earlier.

- **Premature menopause** occurs age 30–40 and is mostly idiopathic, but can also occur after radiation therapy or surgical oophorectomy.
- **Premature ovarian failure** occurs age <30 and may be associated with autoimmune disease or Y chromosome mosaicism.

The etiology of menopausal symptoms is lack of estrogen.

Diagnosis. The laboratory diagnosis of menopause is made through serial identification of elevated gonadotropins.

Clinical Findings. The majority of menopausal symptoms and signs are caused by a lack of estrogen.

- **Amenorrhea** (**most common symptom** is secondary amenorrhea): menses typically become anovulatory and decrease during a period of 3–5 years known as perimenopause.
- **Hot flashes** (75% of menopausal women): unpredictable profuse sweating and sensation of heat, probably mediated through the hypothalamic thermoregulatory center. Obese women are less likely to undergo hot flashes, owing to peripheral conversion of androgens to estrone in their peripheral adipose tissues.
- **Reproductive tract.** Low estrogen leads to decreased vaginal lubrication, increased vaginal pH, and increased vaginal infections.
- **Urinary tract.** Low estrogen leads to increased urgency, frequency, nocturia, and urge incontinence.
- **Psychic.** Low estrogen leads to mood alteration, emotional lability, sleep disorders, and depression.
- **Cardiovascular disease** (**most common cause of mortality** (50%) in postmenopausal women). Prevalence rises rapidly after menopause.
- **Osteoporosis**, a disorder of decreased bone density, leads to pathologic fractures when density falls below fracture threshold

Osteoporosis

The most common bone type of osteoporosis is trabecular bone. The **most common anatomic site** is in the vertebral bodies, leading to crush fractures, kyphosis, and decreased height. Hip and wrist fractures are the next most frequent sites.

Diagnosis. The **most common** method of assessing bone density is with a **DEXA** scan (dual-energy x-ray absorptiometry). The **most common** method of assessing **calcium loss** is 24-h urine hydroxyproline or NTX (N-telopeptide, a bone breakdown product).

The **most common risk factor** is positive family history in a thin, white female. Other risk factors are steroid use, low calcium intake, sedentary lifestyle, smoking, and alcohol.

Prevention. Maximum bone density is found in the mid-20s. Maintenance of bone density is assisted by both lifestyle and medications.

GYN Triad

Premature Ovarian Failure
r/o Y Chromosome Mosaic

- Hot flashes, sweats
- Age 25 years
- ↑ FSH level

Table II-12-4. Osteoporosis

Lifestyle	Ca^{2+} and vitamin D intake
	Weight-bearing exercise
	Stop cigarettes and alcohol
Medical	Historic gold standard for comparing therapies: estrogen replacement
	Inhibit osteoclasts: bisphosphonates (alendronate, risedronate)
	Increase bone density: SERMs (raloxifene)

Definition of abbreviations: SERMS, selective estrogen receptor modulators.

- **Lifestyle.** Calcium and vitamin D intake, weight-bearing exercise, and elimination of cigarettes and alcohol.
- **Medications.** Bisphosphonates (e.g., alendronate, risedronate) inhibit osteoclastic activity. Selective estrogen receptor modulators (SERMs; e.g., raloxifene) increase bone density. Bisphosphonates and SERMs are the first choices for osteoporosis treatment. Calcitonin and fluoride have also been used. While estrogen is a highly effective therapy, it should not be primarily used to treat osteoporosis because of concerns detailed in the next paragraph.

Hormone Replacement Therapy

There are both **benefits** and **risks** associated with hormone replacement therapy.

- Estrogen therapy continues to be the most effective and FDA-approved method for relief of menopausal vasomotor symptoms (hot flashes), as well as genitourinary atrophy and dyspareunia.
- The Women's Health Initiative (WHI) study of the National Institutes of Health (NIH) studied 27,000 postmenopausal women with mean age 63. These included women with a uterus on hormone therapy (HT), both estrogen and progestin, and hysterectomized women on estrogen therapy (ET) only.

Table II-12-5. Critique of Women's Health Initiative Study

Excludes patients with vasomotor symptoms Primary indication for hormone replacement
Mean patient age was 63 years Missed the 10-year "window of opportunity"
Same dose of hormone for all ages Older women don't need as a high dose as do younger women
Patients were not all healthy Hypertension (40%), ↑ cholesterol (15%), diabetes mellitus (7%), myocardial infarction (3%)

GYN Triad

Limitations of WHI

- Women with prominent vasomotor symptoms, the most common reason for initiating HT, were excluded from the study.
- The mean age of 63 was 10 years past the age that most women begin HT, thus missing the "window of opportunity" immediately after menopause.
- The same hormone dose was used in both older and younger women.

- **Benefits:** Both HT and ET groups in WHI had decreased osteoporotic fractures and lower rates of colorectal cancer.
- **Risks:** Both HT and ET groups in WHI were found to have small increases in deep vein thrombosis (DVT). The HT group also had increased heart attacks and breast cancer, but these were not increased in the ET group.

Table II-12-6. WHI–Benefit and Risk (Mean Age of 63 Years)

	Estrogen and Progestin	Estrogen Only
Vaginal dryness	Benefit	Benefit
Hot flashes	Benefit	Benefit
Vasomotor symptoms	Benefit	Benefit
Osteoporosis	Benefit	Benefit
Breast cancer	Risk	No change
Heart disease	Risk	No change
Stroke	Risk	Risk

Estrogen can be administered by oral, transdermal, vaginal, or parenteral routes. All routes will yield the benefits described.

- The **most common current regimen** is oral estrogen and progestin given continuously.
- Women without a uterus can be given continuous estrogen.
- All women with a uterus should also be given progestin therapy to prevent endometrial hyperplasia.

Contraindications for hormone replacement therapy include personal history of an estrogen-sensitive cancer (breast or endometrium), active liver disease, active thrombosis, or unexplained vaginal bleeding.

In 2013, the **Global Consensus Statement on Menopausal Hormonal Therapy (MHT)** by the International Menopause Society made the following recommendations.

Proven Benefits of MHT and Only Indications For Use.

- **Vasomotor symptoms.** MHT is the most effective treatment for vasomotor symptoms associated with menopause at any age, but benefits are more likely to outweigh risks for symptomatic women age <60 or within 10 years after menopause.
- **Vaginal dryness.** Local low-dose estrogen therapy is preferred for women whose symptoms are limited to vaginal dryness or associated discomfort with intercourse.
- **Premature menopause.** In women with premature ovarian insufficiency, systemic MHT is recommended at least until the average age of the natural menopause.

Benefits of MHT but Not Indications For Use.

- **Osteoporosis.** MHT is effective and appropriate for the prevention of osteoporosis-related fractures in at-risk women age <60 or within 10 years after menopause.
- **Coronary heart disease.** Findings depend on the kind of MHT used.
  - **Estrogen-alone** (ET) may decrease coronary heart disease and all-cause mortality in women age <60 and within 10 years of menopause.
  - **Estrogen plus progestogen** (HT) in this age group shows a similar trend for decreased mortality but no significant increase or decrease in coronary heart disease has been found.

Risks of MHT.

- The **risk of venous thromboembolism (VTE) and ischemic stroke** increases with oral MHT but the absolute risk is rare age <60. Observational studies point to a lower risk with transdermal therapy.
- The **risk of breast cancer** in women age >50 associated with MHT is a complex one. The increased risk of breast cancer is primarily associated with the addition of a progestogen to estrogen therapy (HT) and related to the duration of use. The risk of breast cancer attributable to HT is small and decreases after treatment is stopped. Current safety data do not support the use of MHT in breast cancer survivors.

Administration of Menopausal Hormone Therapy (MHT).

- **Uterus present or absent.** Estrogen as a single systemic agent (ET) is appropriate in women after hysterectomy, but additional progestogen (HT) is required in the presence of a uterus.
- **Individualized management.** The option of MHT is an individual decision in terms of quality of life and health priorities, as well as personal risk factors such as age, time since menopause, and risk of venous thromboembolism, stroke, ischemic heart disease, and breast cancer.
- **Dose and duration.** Dose and duration of MHT should be consistent with treatment goals and safety issues, and thus should be individualized.
- **Bioidentical hormones.** The use of custom-compounded bioidentical hormone therapy is not recommended.

Estrogen alternatives

In patients with contraindications to estrogen-replacement therapy, **SERMs** can be used. These are medications with estrogen agonist effects in some tissues and estrogen antagonist effects on others. Although protective against the heart as well as bone, these medications do not have much effect on hot flashes and sweats.

- **Tamoxifen** is a SERM with endometrial and bone agonist effects, but breast antagonist effects.
- **Raloxifene** has bone agonist effects, but endometrial antagonist effects.

The Female Breast 13

Learning Objectives

- ❑ Describe normal breast development
- ❑ Differentiate between benign breast disorders and breast cancer, in terms of diagnosis and treatment

NORMAL BREAST DEVELOPMENT

Embryology

Breasts begin developing in the embryo about 7–8 weeks after conception, consisting only of a thickening or ridge of tissue.

- From weeks 12–16, tiny groupings of cells begin to branch out, laying the foundation for future **ducts** and milk-producing **glands**. Other tissues develop into muscle cells that will form the nipple (the protruding point of the breast) and areola (the darkened tissue surrounding the nipple).
- In the later stages of pregnancy, maternal hormones cause fetal breast cells to organize into branching, tube-like structures, thus forming the milk ducts. In the final 8 weeks, lobules (milk-producing glands) mature and actually begin to secrete a liquid substance called colostrum.
- In both female and male newborns, swellings underneath the nipples and areolae can easily be felt, and a clear liquid discharge (colostrum) can be seen.

Puberty

From infancy to just before puberty, there is no difference between female and male breasts.

- With the beginning of female puberty, however, the release of estrogen—at first alone, and then in combination with progesterone when the ovaries are functionally mature—causes the breasts to undergo dramatic changes that culminate in the fully mature form.
- This process, on average, takes 3–4 years and is usually complete by age 16.

Anatomy

The breast is made of lobes of glandular tissue with associated ducts for transfer of milk to the exterior and supportive fibrous and fatty tissue. On average, there are 15–20 lobes in each breast, arranged roughly in a wheel-spoke pattern emanating from the nipple area. The distribution of the lobes, however, is not even.

- There is a preponderance of glandular tissue in the upper outer portion of the breast. This is responsible for the tenderness in this region that many women experience prior to their menstrual cycle.

Note

Refer to chapter 1 for a discussion of Tanner stages.

- About 80–85% of normal breast tissue is fat during the reproductive years. The 15–20 lobes are further divided into lobules containing alveoli (small sac-like features) of secretory cells with smaller ducts that conduct milk, to larger ducts, and finally to a reservoir that lies just under the nipple. In the nonpregnant, nonlactating breast, the alveoli are small.
- During pregnancy, the alveoli enlarge. During lactation, the cells secrete milk substances (proteins and lipids). With the release of oxytocin, the muscular cells surrounding the alveoli contract to express the milk during lactation.
- Ligaments called **Cooper's ligaments**, which keep the breasts in their characteristic shape and position, support breast tissue. In the elderly or during pregnancy, these ligaments become loose or stretched, respectively, and the breasts sag.
- The lymphatic system drains excess fluid from the tissues of the breast into the axillary nodes. Lymph nodes along the pathway of drainage screen for foreign bodies such as bacteria or viruses.

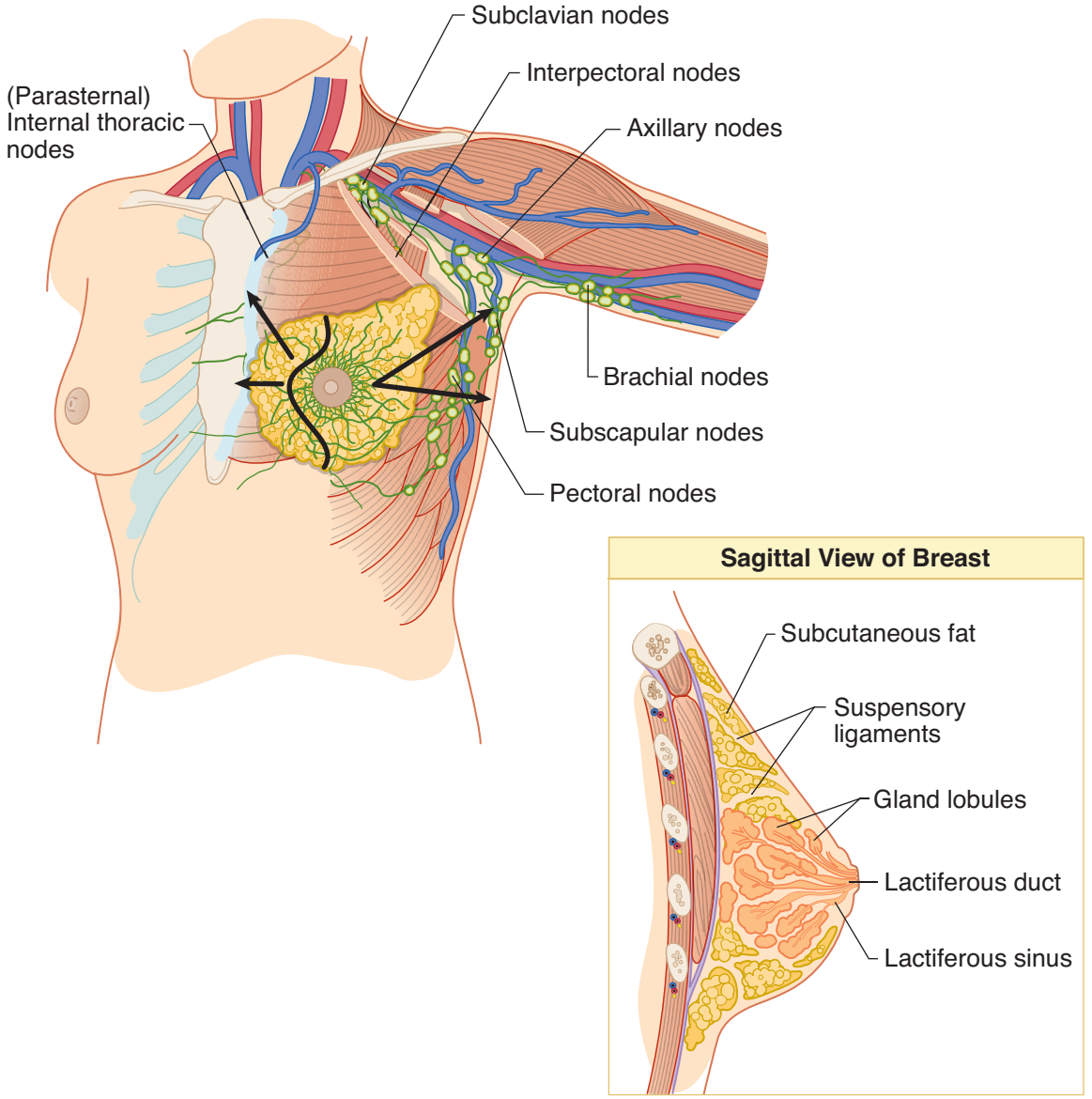


Figure II-13-1. Breast

Hormones

Reproductive hormones are important in the development of the breast in puberty and in lactation.

- **Estrogen**, released from the ovarian follicle, promotes the growth ducts.
- **Progesterone**, released from the corpus luteum, stimulates the development of milk-producing alveolar cells.
- **Prolactin**, released from the anterior pituitary gland, stimulates milk production.
- **Oxytocin**, released from the posterior pituitary in response to suckling, causes milk ejection from the lactating breast.

Lactation

- The breasts become fully developed under the influence of **estrogen**, **progesterone**, and **prolactin** during pregnancy. **Prolactin** causes the production of milk, and **oxytocin** release (via the suckling reflex) causes the contraction of smooth-muscle cells in the ducts to eject the milk from the nipple.
- The first secretion of the mammary gland after delivery is colostrum. It contains more protein and less fat than subsequent milk, and contains IgA antibodies that impart some **passive immunity** to the infant. Most of the time it takes 1–3 days after delivery for milk production to reach appreciable levels.
- The expulsion of the placenta at delivery initiates milk production and causes the drop in circulating estrogens and progesterone. **Estrogen** antagonizes the positive effect of prolactin on milk production.
- The physical stimulation of suckling causes the release of oxytocin and stimulates prolactin secretion, causing more milk production.

Mammography

Mammography is an outpatient office radiologic procedure.

- Mammography may be a screening test for breast cancer when performed on asymptomatic women. Screening typically uses 2 views of each breast: **craniocaudal** and **lateral**. The patient is encouraged to lean in toward the device to image as much of the breast tissue as possible.
- Recommended **age to start mammograms** varies among medical organizations, ranging from age 40–50.
  - **Start screening at age 40** gives potentially earlier cancer diagnosis (benefit) but at the cost of higher false-positives with unnecessary follow-up testing and anxiety (harms). False-negatives occur more in younger women and those with denser breasts.
  - **Start screening at age 50** gives fewer false-negatives (benefit) but at a cost of potentially later diagnosis (harm).
  - The best strategy is for doctors to assess individual patient risk and engage in **shared decision-making** with the patient.
- Mammography may also be performed because of a breast complaint (e.g., breast mass, nipple discharge, abnormal screening mammogram); in those cases many images are taken, some under higher magnification to better visualize the target area.
- **Risks:** ionizing radiation exposure 0.7 mSv (about the same that the average person receives from background radiation in three months [1 Rad = 10 mSv])

Note

The conflicting recommendations for age to start mammography are the result of differing views of "harm versus benefit" studies.

BENIGN BREAST DISORDERS

Cystic Breast Mass

A 40-year-old menstruating woman had a 2 cm cystic breast mass confirmed by breast ultrasonography.

Note

Mammograms are discussed in detail in Gynecology, chapter 1.

Diagnosis. Cyst aspiration and fine-needle aspiration are important components in the preliminary diagnosis of breast disorders. Fine-needle aspiration of a palpable macrocyst, the appropriate procedure for this patient, can be performed in an office setting. Interpretation of fine-needle aspiration requires the availability of a trained cytopathologist.

Management. Preaspiration mammography should be obtained. If the cyst disappears and the cytology is benign, no further workup is required.

Fibrocystic Breast Changes

A 30-year-old woman experiences bilateral breast enlargement and tenderness, which fluctuates with her menstrual cycle. On physical examination the breast feels lumpy, and the patient indicates a sensitive area with a discrete 1.5 cm nodule, which she says is consistently painful. A fine-needle aspiration is performed, and clear fluid is withdrawn. Clinically the cysts resolved.

Diagnosis. Cyclic premenstrual mastalgia is often associated with fibrocystic changes of the breast, a condition that is no longer considered a disease but a heterogeneous group of disorders. Breast discomfort may be accompanied by a palpable mass. Fine-needle aspiration can easily distinguish whether a mass is solid or cystic. The procedure requires no special skill other than stabilizing the mass so that needle aspiration can be done with precision. The goal of cyst aspiration is complete drainage of the cyst with collapse of the cyst wall.

Management.

- **Mass disappears.** If the cyst fluid is clear, it may be discarded. If the cyst fluid is grossly bloody, it should be sent for cytologic examination to rule out the possibility of intracystic carcinoma. After aspiration, the affected area must be palpated to determine whether there is a residual mass. If there is no residual mass, the patient may be reexamined in 4–6 weeks for the reaccumulation of fluid. If fluid reaccumulates, it may be aspirated again.
- **Mass persists.** A mass that persists requires further workup. A persistent accumulation is managed by mammography and excision. Because changes such as hematoma related to aspiration may affect mammographic appearances, it is recommended that mammography not be performed until two weeks after aspiration. Definitive evaluation of a persistent mass requires excisional biopsy.
- **Conservative.** Ultrasonography is useful in distinguishing cysts from solid masses. If ultrasonography has been performed before aspiration and has shown a cyst with distinct smooth contours, an alternative management plan would be conservative follow-up with serial ultrasound scans. If the cyst disappears on aspiration and the fluid is clear, no further workup is required.

Breast Fibroadenoma

A 25-year-old woman visits the gynecologist for routine annual examination. During the examination she has a palpable, rubbery breast mass, which has been present and stable for the past two years. The pathology report of fine-needle aspiration was consistent with fibroadenoma.

Diagnosis. Fibroadenomas are the **most common breast tumors** found in adolescents and young women. In approximately 15% of patients they occur as multiple lesions. Clinically, fibroadenomas are discrete, smoothly contoured, rubbery, nontender, freely moveable masses. The most distinctive gross feature of fibroadenomas that allows them to be distinguished from other breast lumps is their mobility. Fibroadenomas arise from the epithelium and stroma of the terminal duct lobular unit, most frequently in the upper outer quadrant of the breast. An association of fibroadenomas with the development of breast cancer has not been well established. Any associated increases in breast cancer risk depends on the presence of proliferative changes in the fibroadenoma itself or in the surrounding breast and on a family history of breast carcinoma.

Although cysts and fibroadenomas may be indistinguishable on palpation, ultrasound examination easily distinguishes cystic from solid lesions. On fine-needle aspiration, cysts typically collapse, whereas samples from a fibroadenoma present a characteristic combination of epithelial and stromal elements.

Management.

- **Conservative.** Some clinicians advocate conservative management of fibroadenomas, especially in young women, because they can be diagnosed by ultrasonography and core-needle biopsy or fine-needle aspiration with a high degree of confidence, and in some cases they will resolve. A survey of patient preferences, however, has revealed that many women choose excisional biopsy even when they are assured that the lesion is benign by fine-needle aspiration.
- **Excision.** Typically, the lesion is "shelled out" with a surrounding thin rim of breast tissue to avoid the necessity of re-excision in the rare instances when the tumor proves to be a **phyllodes tumor**. This is a mixed epithelial and stromal tumor that has benign, borderline, and malignant variants. The biology of the phyllodes tumor is determined by its stromal elements; in its fully malignant form, it behaves as a sarcoma.

Mammography Microcalcifications

A 45-year-old woman visits her gynecologist after having her yearly mammogram done. The mammogram reveals a "cluster" of microcalcifications.

Diagnosis. A geographic cluster of microcalcifications is nonpalpable. Although most of these lesions are benign, approximately 15–20% represent early cancer. An occult lesion requires stereotactic needle localization and biopsy under mammographic guidance. The coordinates of the lesion are calculated by the computer according to the basic principles of stereotaxis. The radiologist selects the length of the biopsy needle, and a core biopsy is obtained. The procedure is performed in an outpatient setting.

Management. Treatment is based on the established histologic diagnosis.

Persistent Breast Mass

A 35-year-old woman has a persistent breast mass after a fine-needle aspiration has been performed. The breast mass is confirmed by ultrasonography.

Diagnosis. With the combination of physical examination, fine-needle aspiration or core biopsy, and mammography, open biopsies are being performed less frequently. Excisional biopsy has the advantage of a complete evaluation of the size and histologic characteristics of the tumor before definitive therapy is selected. An excisional biopsy is usually recommended in the following circumstances:

- Cellular bloody cyst fluid on aspiration
- Failure of a suspicious mass to disappear completely upon fluid aspiration
- Bloody nipple discharge, with or without a palpable mass
- Skin edema and erythema suggestive of inflammatory breast carcinoma, and a needle core biopsy cannot be performed

In the past, recurrent or persistent simple breast cysts were routinely excised. Because of improvement in ultrasonographic technology, these cysts may now be followed conservatively. This patient, who has had a fine-needle aspiration before, is a candidate for an excisional biopsy.

Management. Treatment is based on the established histologic diagnosis.

Bloody Nipple Discharge

A 60-year-old woman comes to the gynecologist's office complaining of a left breast bloody nipple discharge.

Diagnosis. A bloody nipple discharge usually results from an intraductal papilloma. The treatment is total excision of the duct and papilloma through a circumareolar incision. Modern ductography does not reliably exclude intraductal pathology and is not a substitute for surgery in patients with pathologic discharge. Its utility is in identifying multiple lesions or lesions in the periphery of the breast.

Management. Treatment is based on the established histologic diagnosis.

BREAST CANCER

A 65-year-old woman visits the gynecologist with a solid 2 cm mass in the upper outer quadrant of the left breast. A biopsy of the lesion is done, which is consistent with "infiltrating ductal breast cancer."

Breast cancer continues to be the **most common cancer** diagnosed in women of western industrialized countries. In 2018, an estimated 266,00 new cases of invasive breast cancer are expected to be diagnosed in women in the United States, along with 64,000 new cases of non-invasive (in situ) breast cancer.

Management. The preferred treatment for most patients with stage I or II breast cancer is considered to be breast-conserving therapy with a wide excision, axillary lymph node dissection or sentinel lymph node biopsy, and radiotherapy. Lymphatic mapping and sentinel lymph node biopsy are new procedures that offer the ability to avoid axillary lymph node dissection and its associated morbidity in patients with small primary tumors who are at low risk of axillary node involvement, while still offering nodal staging information.

Prognostic Factors. Some of the key decisions in the current management of primary breast cancer involve the need for prognostication. Prognostic factors serve to identify those patients who might benefit from adjuvant therapy.

- **Lymph node status.** This is important in determining cancer staging and treatment options. Axillary lymph node status is the most important factor in the prognosis of patients with breast cancer. As the number of positive axillary lymph nodes increases, survival rate decreases and relapse rate increases. An adequate dissection usually contains at least 10 lymph nodes; however, because these tumors in 25–30% of patients with negative nodes eventually recur, other biologic prognostic factors also are needed.
- **Tumor size.** This correlates with the number of histologically involved lymph nodes; however, it is also an independent prognostic factor, particularly in node-negative women. The use of size of the tumor as the most significant prognostic factor is problematic because 15% of patients with small tumors have positive nodal involvement.
- **Receptor status.** It is standard practice to determine both estrogen and progesterone receptor status at the time of diagnosis for definitive surgical therapy. Although hormone receptor status correlates with the prognosis, it does so to a lesser degree than nodal status. Hormone receptor determination is, however, of critical importance as a predictive factor. A predictive factor is any measurement associated with response or lack of response of a particular therapy.
  - Estrogen receptor status has clearly shown to be a predictive factor for hormone therapy, either in the adjuvant therapy or the metastatic disease setting. **HER-2** (also known as HER-2.neu and c-erbB-2) is an epidermal growth factor receptor on the surface of a cell that transmits growth signals to the cell nucleus.
  - Approximately 25–30% of breast cancers overexpress HER-2, and overexpression of the receptor is associated with poor prognosis. This may be more of a reflection of the biologic correlates of HER-2 overexpression, e.g., rapid tumor cell proliferation, larger tumor size, and loss of hormone receptors, than an independent prognostic indicator.
- **DNA ploidy status.** DNA ploidy status of tumors is determined by flow cytometry. It measures the average DNA per cell. Tumors can be classified as diploid with normal DNA content or aneuploid. Disease-free survival rates are significantly worse in patients with aneuploid tumors than in those with diploid tumors; however, it is unclear whether ploidy has an independent prognostic value.

Infiltrating Ductal Carcinoma

This is the **most common breast malignancy**, accounting for 80% of breast cancers. Most are unilateral and start as atypical ductal hyperplasia, which may progress to ductal carcinoma in situ (DCIS), which then may break through the basement membrane and progress to invasive ductal carcinoma. Over time the tumor will become a stony hard mass as it increases in size and undergoes a fibrotic response.

Infiltrating Lobular Carcinoma

This is the **second most common breast malignancy**, accounting for 10% of breast cancers. Most are unilateral and start as lobular carcinoma in situ (LCIS), which then may break through the basement membrane and progress to invasive lobular carcinoma. The prognosis is better with lobular than with ductal carcinoma.

Inflammatory Breast Cancer

This is an uncommon breast malignancy that can mimic **mastitis**. Usually, there is no single lump or tumor. It is characterized by rapid growth with early metastasis. As the lymphatics get blocked, the breast becomes erythematous, swollen, and warm to examination. The edematous skin of the breast appears pitted, like the skin of an orange, giving the classic **peau d'orange** appearance.

Paget Disease of the Breast/Nipple

This is an uncommon breast malignancy with a generally better prognosis than infiltrating ductal carcinoma. The lesion is pruritic and appears red and scaly; it is often located in the nipple spreading to the areola. The skin appearance can mimic dermatosis like eczema or psoriasis. The nipple may become inverted and discharge may occur. It is almost always associated with DCIS or infiltrating ductal carcinoma.

Breast Cancer Risk Factors

BRCA 1 or 2 gene mutation	RR 15
Ductal or Lobular CIS	RR 15
Atypical hyperplasia	RR 4
Breast irradiation age <20	RR 3
Positive family history	RR 3

Sentinel Node Biopsy

A sentinel node (SLN) is the first lymph node(s) to which cancer cells are likely to spread from the primary tumor. Cancer cells may appear in the sentinel node before spreading to other lymph nodes. A dye is injected near the tumor to allow flow to the SLN. A biopsy of the dye-stained node is performed to help determine the extent or stage of cancer. Because SLN biopsy involves the removal of fewer lymph nodes than standard lymph node removal procedures, the potential for side effects is lower.

Node-Positive Early Breast Cancer

> A healthy 55-year-old woman had a lumpectomy (negative margins) and axillary node dissection for a 2.5 cm tumor in the upper outer quadrant of the left breast, with three positive lymph nodes. The tumor was positive for both estrogen and progesterone receptors. She comes to the gynecologist's office wanting an opinion about further therapy.

Breast-conserving therapy with a wide excision (lumpectomy), axillary dissection (or sentinel node biopsy), and radiation therapy are considered the preferred treatment for most patients with stage I or II breast cancer.

In patients at moderate or high risk of developing systemic metastasis, it is preferable to give adjuvant therapy, beginning with chemotherapy followed by radiation therapy.

This patient has a high risk of recurrence because of the presence of lymph node metastasis, and it would be inappropriate to withhold further therapy. Another high risk factor here is that her tumor is larger than 1 cm.

A large number of prospective randomized trials, as well as recent overviews and meta-analysis of adjuvant systemic therapy, have determined that both chemotherapy and tamoxifen therapy reduce the odds of recurrence in breast cancer patients. A few randomized clinical trials and the overview of meta-analysis of randomized clinical trials have suggested that the combination of chemotherapy and tamoxifen is superior to chemotherapy alone or tamoxifen alone in post-menopausal patients with node-positive breast cancer. Women with estrogen receptor-negative breast cancer appear to have no improvement in recurrence or survival from tamoxifen use.

It has been established that combination chemotherapy is superior to single-agent therapy, and that 4–6 cycles of combination therapy are as effective as >6 cycles of treatment.

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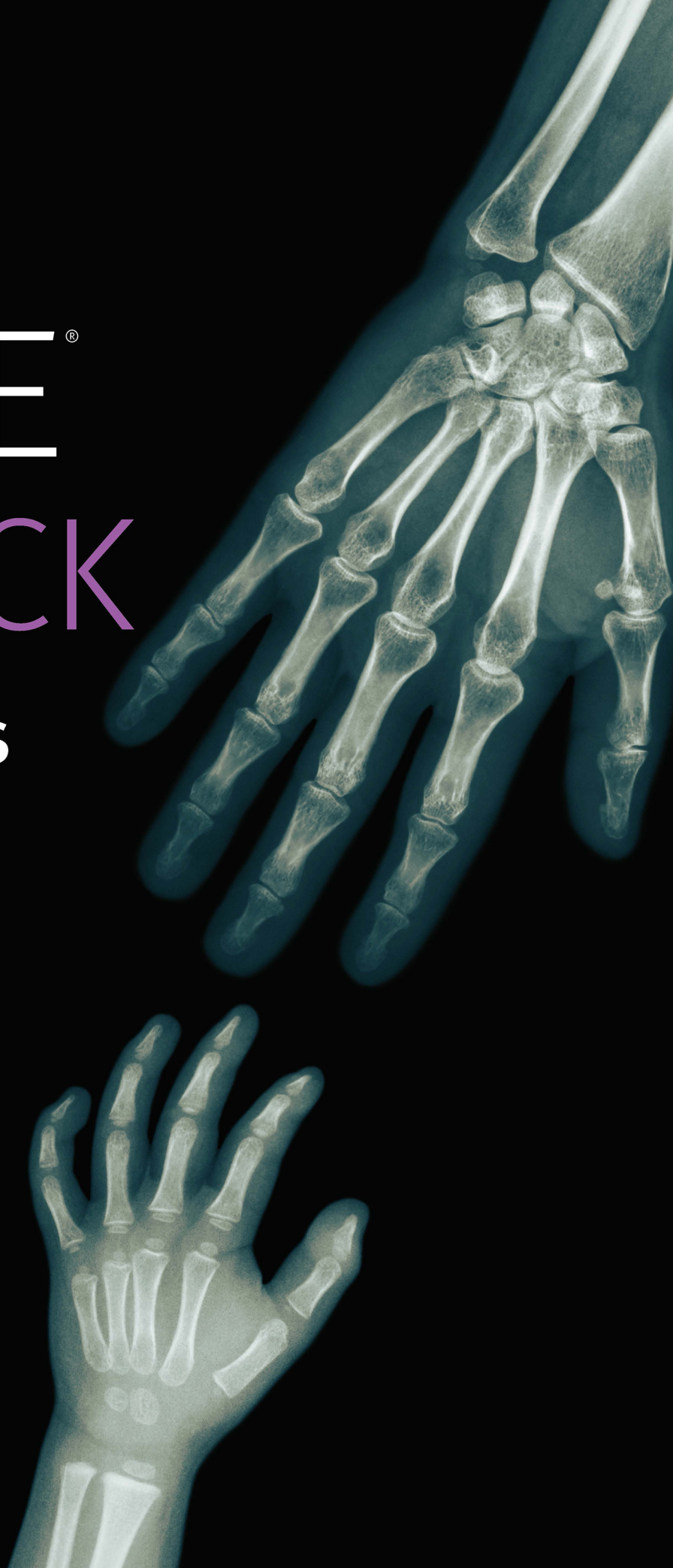

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The Newborn 1

Learning Objectives

- ❑ Calculate an Apgar score
- ❑ Use knowledge of birth injuries to predict symptomology
- ❑ Demonstrate understanding of newborn screening, fetal growth/maturity, and neonatal infections

APGAR SCORE

A newborn infant at birth is noted to have acrocyanosis, heart rate 140/min, and grimaces to stimulation. She is active and has a lusty cry. What is her Apgar score?

Table 1-1. Apgar Scoring System

Evaluation	0 Points	1 Point	2 Points
Heart rate	0	‹100/min	›100/min
Respiration	None	Irregular, shallow, gasps	Crying
Color	Blue	Pale, blue extremities	Pink
Tone	None	Weak, passive	Active
Reflex irritability	None	Facial grimace	Active withdrawal

Apgar scores are routinely assessed at 1 and 5 minutes, and every 5 minutes thereafter as long as resuscitation is continuing.

- The **1-minute score** gives an idea of what was going on during labor and delivery.
- The **5-minute score** gives an idea of response to therapy (resuscitation).

In general, the Apgar score is *not* predictive of outcome; however, infants with score 0–3 at ≥5 minutes compared to infants with score 7–10 have a worse neurologic outcome.

Newborn Care

- Vitamin K IM
- Prophylactic eye erythromycin
- Umbilical cord care
- Hearing test
- Newborn screening tests

BIRTH INJURIES

On physical exam, a 12-hour-old newborn is noted to have nontender swelling of the head that does not cross the suture line. What is the most likely diagnosis?

Table 1-2. Common Injuries During Deliveries

Injury	Specifics	Outcome
Skull fractures	In utero from pressure against bones or forceps; **linear:** most common	• Linear: no symptoms and no treatment needed • **Depressed:** elevate to prevent cortical injury
Brachial palsy	**Erb-Duchenne:** C5–C6; cannot abduct shoulder; externally rotate and supinate forearm; **Klumpke:** C7–C8 ± T1; paralyzed hand ± Horner syndrome	Most with full recovery (months); depends on whether nerve was injured or lacerated; Rx: proper positioning and partial immobilization; massage and range of motion exercises; if no recovery in 3–6 mo, then neuroplasty
Clavicular fracture	Especially with shoulder dystocia in vertex position and arm extension in breech	Palpable callus within a week; Rx: with immobilization of arm and shoulder
Facial nerve palsy	Entire side of face with forehead; forceps delivery or in utero pressure over facial nerve	Improvement over weeks (as long as fibers were not torn); need eye care; neuroplasty if no improvement (torn fibers)
Caput succedaneum	Diffuse edematous swelling of soft tissues of scalp; **crosses suture lines**	Disappears in first few days; may lead to molding for weeks
Cephalohematoma	Subperiosteal hemorrhage: **does not cross suture lines**	May have underlying linear fracture; resolve in 2 wk to 3 mo; may calcify; jaundice

PHYSICAL EXAMINATION

A newborn infant has a blue-gray pigmented lesion on the sacral area. It is clearly demarcated and does not fade into the surrounding skin. What is the most likely diagnosis?

A newborn has a flat, salmon-colored lesion on the glabella, which becomes darker red when he cries. What is the best course of management?

Table 1-3. Physical Examination—Common Findings

Finding/Diagnosis	Description/Comments
SKIN	
Cutis marmorata	Lacy, reticulated vascular pattern over most of body when baby is cooled; improves over first month; abnormal if persists
Salmon patch (nevus simplex)	Pale, pink vascular macules; found in nuchal area, glabella, eyelids; usually disappears
Mongolian spots	Blue to slate-gray macules; seen on presacral, back, posterior thighs; › in nonwhite infants; arrested melanocytes; usually fade over first few years; *differential*: child abuse
Erythema toxicum, neonatorum	Firm, yellow-white papules/pustules with erythematous base; peaks on second day of life; contain eosinophils; benign
Hemangioma	**Superficial**: bright red, protuberant, sharply demarcated; most often appear in first 2 months; most on face, scalp, back, anterior chest; rapid expansion, then stationary, then involution (most by 5–9 years of age); Rx: beta blockers, embolization; **deeper**: bluish hue, firm, cystic, less likely to regress; Rx: (steroids, pulsed laser) only if large and interfering with function
HEAD	
Preauricular tags/pits	Look for hearing loss and genitourinary anomalies.
Coloboma of iris	Cleft of lid, iris, lens, retina, or choroid. In iris, manifests as keyhole appearance at the 6 o'clock position. May be autosomal-dominant or part of CHARGE syndrome.
Leukocoria—white reflex	Retinoblastoma; cataract; retinopathy of prematurity; retinal detachment; larval granulomatosis
Aniridia	Hypoplasia of iris; defect may go through to retina; association with Wilms tumor
EXTREMITIES	
Polydactyly	Extra digit, partial digit, or cleft digit after the 4th finger (ulnar side); world's most common minor malformation; usually surgically removed at 1–2 years of age

NEWBORN SCREENING

A 1-month-old fair-haired, fair-skinned baby presents with projectile vomiting of 4 days' duration. Physical exam reveals a baby with eczema and a musty odor. Which screening test would most likely be abnormal?

As per the American College of Medical Genetics, every newborn is screened for a core panel of 29 disorders, with an additional 25 recommended (Expanded Newborn Screening Program; varies per state).

- All states now use tandem mass spectrometry; typically done after 24–48 hrs of feedings prior to baby leaving the birth hospital
- With early discharge, may be performed at first postnatal visit (3–5 days) for improved accuracy
- In addition to a heel stick blood sample, current program also includes a hearing test and pulse oximetry for critical congenital heart disease.

Examples of the more common disorders in the expanded program include:

- Phenylketonuria, tyrosinemia type I, 21-hydroxylase deficiency, classic galactosemia
- HbS/β-thal, Hb SS, HbS/HbC
- Congenital hypothyroidism
- Cystic fibrosis

Table 1-4. Two Newborn Screening Diseases*

	Phenylketonuria (PKU)	Classic Galactosemia
Defect	Phenylalanine hydroxylase; accumulation of PHE in body fluids and central nervous system	Gal-1-P uridylyltransferase deficiency; accumulation of gal-1-P with injury to **kidney, liver, and brain**
Presentation	**Intellectual disability** vomiting, growth retardation, purposeless movements, athetosis, seizures	**Jaundice (often direct),** hepatomegaly, vomiting, **hypoglycemia**, **cataracts**, seizures, poor feeding, poor weight gain, **intellectual disability**
Associations	**Fair hair, fair skin, blue eyes**, tooth abnormalities, microcephaly	**Predisposition to *E. coli* sepsis**; developmental delay, speech disorders, learning disabilities
Other comments	**Normal at birth**; gradual MR over first few months	**May begin prenatally—transplacental galactose from mother**
Treatment	Low PHE diet for life	No lactose—reverses growth failure, kidney and liver abnormalities and cataracts, **but not neurodevelopmental problems**

G-1-P, galactose-1-phosphate; PHE, phenylalanine

*Items in **bold** have a greater likelihood of appearing on the exam.

Hearing Loss

Pediatric hearing loss is more prevalent than diabetes mellitus and all childhood cancers. A universal newborn hearing screening is recommended prior to newborn discharge, with the goal of evaluating all hearing loss by age 3 months. Usually the otoacoustic emissions test (OAE) is used, where a small earphone/microphone is placed in the ear and sounds are played.

- If hearing is normal, an echo is reflected back into the ear canal and is measured by the microphone.
- If hearing is not normal (patient does not pass), newborns are given the auditory brainstem response test (ABR) (most accurate hearing measure through age 6 months). Sounds are presented through a small earphone, measured with head electrodes, and analyzed by a computer.
- Normal OAE: intact hearing through the cochlea
- Normal ABR: also establishes the integrity of the auditory nerve

As for the causes of hearing loss, up to 60% prelingual is **genetic** (>60 gene loci, >500 syndromes with hearing loss); 70-80% is autosomal recessive, with 50% having a defect in connexin 26 (a gap junction protein). Examples include Waardenburg syndrome (most common autosomal dominant condition with hearing loss), neurofibromatosis-2 (AD), **Alport syndrome** (AR).

Up to 25% are nongenetic and up to 25% are idiopathic. Examples include **CMV** (most common congenital cause; then other congenital infections); otitis media with effusion (**OME**) (most common childhood cause); bacterial meningitis, especially **pneumococcus** (occurs early and in >30%); trauma, especially to temporal bone; medication (**aminoglycosides, loop diuretics**, cisplatin); acoustic (loud music, especially with earbuds/phones; audiograms show **high-frequency loss at 4,000 Hz**).

FETAL GROWTH AND MATURITY

Table 1-5. Intrauterine Growth Restriction (IUGR)

Type	Reason	Main Etiologies	Complications
Symmetric	Early, in utero insult that affects growth of most organs	Genetic syndromes, chromosomal abnormalities, congenital infections, teratogens, toxins	Etiology dependent; delivery of oxygen and nutrients to vital organs usually normal
Asymmetric (head sparing)	Relatively late onset after fetal organ development; abnormal delivery of nutritional substances and oxygen to the fetus	Uteroplacental insufficiency secondary to maternal diseases (malnutrition, cardiac, renal, anemia) and/or placental dysfunction (hypertension, autoimmune disease, abruption)	Neurologic (asphyxia) if significant decreased delivery of oxygen to brain

Gestational Age and Size at Birth		
Preterm	**Large for Gestational Age (LGA)—Fetal Macrosomia**	**Post-term**
• Premature—liveborn infants delivered prior to 37 weeks as measured from the first day of the last menstrual period • Low birth weight (<2,500 grams), possibly due to prematurity, IUGR, or both	• Birth weight >4,500 grams at term • Predisposing factors: obesity, diabetes • Higher incidence of birth injuries and congenital anomalies	• Infants born after 42 weeks' gestation from last menstrual period • **When delivery is delayed ≥3 weeks past term, significant increase in mortality** • Characteristics – Increased birth weight – Absence of lanugo – Decreased/absent vernix – Desquamating, pale, loose skin – Abundant hair, long nails – If placental insufficiency, may be meconium staining

ENDOCRINE DISORDERS

Infants of Diabetic Mothers

You are called to see a 9.5-pound newborn infant who is jittery. Physical exam reveals a large plethoric infant who is tremulous. A murmur is heard. Blood sugar is low.

- Maternal hyperglycemia (types I and II DM) → fetal hyperinsulinemia
- Insulin is the major fetal growth hormone → increase in size of all organs except the brain
- Major metabolic effect is at birth with sudden placental separation → **hypoglycemia**
- Infants may be **large for gestational age and plethoric** (ruddy).
- Other **metabolic findings: hypocalcemia and hypomagnesemia** (felt to be a result of delayed action of parathyroid hormone)
- **Common findings**
  - **Birth trauma** (macrosomia)
  - **Tachypnea** (transient tachypnea, respiratory distress syndrome, cardiac failure, hypoglycemia)
  - **Cardiomegaly—asymmetric septal hypertrophy** (insulin effect, reversible)
  - **Polycythemia (and hyperviscosity)** → hyperbilirubinemia → jaundice

  - **Renal vein thrombosis** (flank mass, hematuria, thrombocytopenia) from polycythemia
  - **Increased incidence of congenital anomalies**
    - **Cardiac**—especially VSD, ASD, transposition
    - **Small left colon syndrome** (transient delay in development of left side of colon; presents with abdominal distention)
    - **Caudal regression syndrome:** spectrum of structural neurologic defects of the caudal region of spinal cord which may result in neurologic impairment (hypo, aplasia of pelvis & LE)
- Prognosis—Infants of diabetic mothers are more predisposed to diabetes and LGA infants are at increased risk of childhood obesity.
- Treatment—careful monitoring and glucose control during pregnancy + close monitoring of infant after delivery; early frequent feeds (oral, NG if hypoglycemia continues) followed by IV dextrose if euglycemia has not resulted

Clinical Recall

Which of the following is commonly seen in infants of diabetic mothers?

A. Microsomia

B. Small heart size

C. Polycythemia

D. Renal artery thrombosis

E. Slow respiratory rate

Answer: C

RESPIRATORY DISORDERS

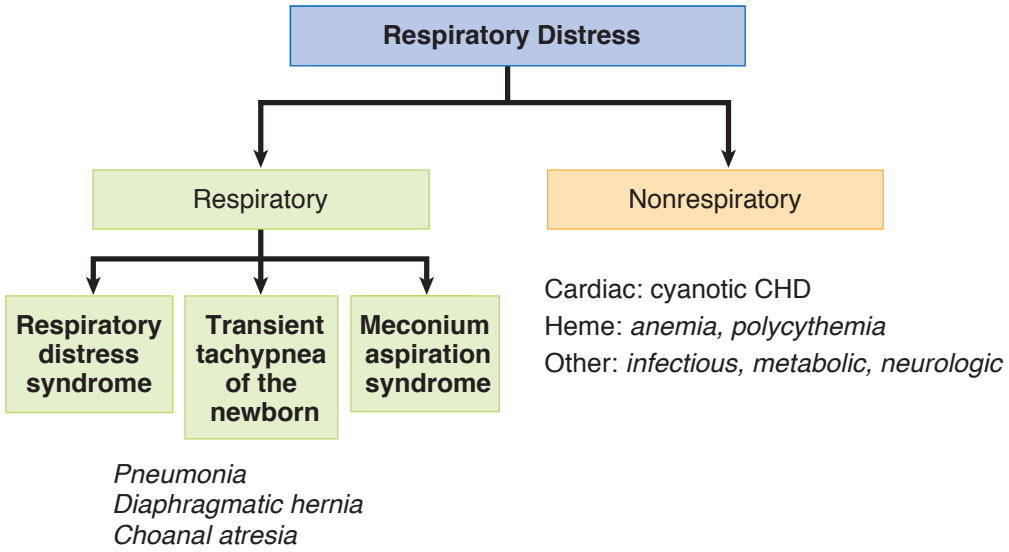

Figure 1-1. Respiratory Distress

Respiratory Distress Syndrome (RDS)

Shortly after birth, a 33-week gestation infant develops tachypnea, nasal flaring, and grunting and requires intubation. Chest radiograph shows a hazy, ground-glass appearance of the lungs.

- Deficiency of **mature surfactant** (surfactant matures over gestation with the addition of phosphatidyl groups; therefore, the incidence of surfactant deficiency diminishes toward term.)
- Inability to maintain alveolar volume at end expiration → decreased functional residual capacity and atelectasis
- Primary initial pulmonary hallmark is **hypoxemia.** Then, **hypercarbia and respiratory acidosis ensue.**
- Diagnosis
  - **Best initial diagnostic test—chest radiograph**
    - Findings: **ground-glass appearance, low lung volume, air bronchograms**
  - **Most accurate diagnostic test—L/S ratio** (part of complete lung profile; lecithin-to-sphingomyelin ratio)
    - Done on amniotic fluid prior to birth
- **Best initial treatment—oxygen**
- **Most effective treatment—intubation and exogenous surfactant administration**
- **Primary prevention**
  - Avoid prematurity (tocolytics)
  - **Antenatal betamethasone**

Transient Tachypnea of the Newborn (TTN)

- Slow absorption of fetal lung fluid → decreased pulmonary compliance and tidal volume with increased dead space
- Tachypnea after birth
- Generally minimal oxygen requirement
- **Common in term infant delivered by Cesarean section or rapid second stage of labor**
- **Chest x-ray (best test)**—air-trapping, fluid in fissures, perihilar streaking
- Rapid improvement generally within hours to a few days

Meconium Aspiration

- Meconium passed as a result of hypoxia and fetal distress; may be aspirated in utero or with the first postnatal breath → airway obstruction and pneumonitis → failure and pulmonary hypertension
- **Chest x-ray (best test)—patchy infiltrates, increased AP diameter, flattening of diaphragm**
- Other complications—air leak (pneumothorax, pneumomediastinum)

- **Prevention—endotracheal intubation and airway suction of depressed infants with thick meconium**
- Treatment—positive pressure ventilation and other complex NICU therapies

Diaphragmatic Hernia

- Failure of the diaphragm to close → abdominal contents enter into chest, causing **pulmonary hypoplasia.**
- Born with respiratory distress and **scaphoid abdomen**
- **Bowel sounds may be heard in chest**
- Diagnosis—prenatal ultrasound; **postnatal x-ray (best test) reveals bowel in chest**
- Best initial treatment—immediate intubation in delivery room for known or suspected CDH, followed by surgical correction when stable (usually days)

GASTROINTESTINAL AND HEPATOBILIARY DISORDERS

See also GI chapter on this topic.

Umbilical Hernia

- Failure of the umbilical ring closure, weakness of abdominal muscles
- Most are small and resolve in 1-2 years without any treatment
- Surgery if getting larger after 1-2 years, symptoms (strangulation, incarceration), and/or persistent after age 4

Omphalocele

- Failure of intestines to return to abdominal cavity with gut through umbilicus at 11 weeks' gestation
- Covered in a sac (protection)
- Associated with other major malformations and possible genetic disorders (trisomy)
- Large defects need a staged reduction (use of a surgical Silo), otherwise respiratory failure and ischemia

Gastroschisis

- Defect in abdominal wall lateral to umbilicus (vascular accident; typically not associated with other malformations)
- Any part of the GI tract may protrude
- Not covered by a sac
- Major problem with the intestines: atresia, stenosis, ischemia, short gut
- Surgery based on condition of gut; if no ischemia, large lesions need a staged reduction as with omphalocele

Necrotizing Enterocolitis (NEC)

- Transmural intestinal necrosis
- Greatest risk factor is prematurity; rare in term infants
- Prematurity + immature gut barrier + enteral feeds + possible microorganisms = NEC
- Symptoms usually related to **introduction of feeds**: bloody stools, apnea, lethargy, and abdominal distention once perforation has occurred
- **Pneumatosis intestinalis** on plain abdominal film is pathognomonic (air in bowel wall)
- Treatment: cessation of feeds, gut decompression, systemic antibiotics, and supportive care; surgical resection of necrotic bowel may be necessary; **early surgical consult is imperative**

Imperforate Anus

- Failure to pass stool after birth
- No anal opening visible
- Treatment is surgical correction.
- May be part of VACTERL association.

Jaundice

A 2-day-old infant is noticed to be jaundiced. He is nursing and stooling well. Indirect bilirubin is 11.2 mg/dL; direct is 0.4 mg/dL. Physical exam is unremarkable except for visible jaundice.

- Pathophysiology
  - Increased production of bilirubin from breakdown of fetal red blood cells plus immaturity of hepatic conjugation of bilirubin and elimination in first week of life
  - Rapidly increasing unconjugated (indirect reacting) bilirubin can cross the blood-brain barrier and lead to **kernicterus** (**unconjugated bilirubin in the basal ganglia and brain stem nuclei**). Hypotonia, seizures, opisthotonos, delayed motor skills, choreoathetosis, and **sensorineural hearing loss** are features of kernicterus.

Note

Work up for pathologic hyperbilirubinemia when:

- It appears on day 1 of life
- Bilirubin rises >5 mg/dL/day
- Bilirubin >13 mg/dL in term infant
- Direct bilirubin >2 mg/dL at any time

Table 1-6. Physiologic Jaundice Versus Pathologic Jaundice

Physiologic Jaundice	Pathologic Jaundice
Appears on second to third day of life (term)	May appear in first 24 hours of life
Disappears by fifth day of life (term)—7th	Variable
Peaks at second to third day of life	Variable
Peak bilirubin ‹13 mg/dL (term)	Unlimited
Rate of bilirubin rise ‹5 mg/dL/d	Usually ›5 mg/dL/d

The **causes of hyperbilirubinemia** with respect to **bilirubin metabolism** are as follows:

- RBC metabolism
  - Increased RBCs
    - Physiologic jaundice (healthy newborn [normal Hct 42–65])
    - Polycythemia (Hct >65)
      i. **Increased RBC production:** Chronic hypoxia, IUGR, post-mature; IODM, Beckwith-Wiedemann syndrome (insulin effect); trisomies (unknown mechanism)
      ii. **Extra RBCs entering the circulation:** delayed cord clamping, twin-twin transfusion
      iii. Treatment: partial exchange transfusion with normal saline (dilutional)
  - Increased hemolysis
    - **Immune-mediated** (labs: high unconjugated bilirubin, may be anemia, increased reticulocyte count, **positive direct Coombs test**)
      i. Rh negative mother/Rh positive baby: classic hemolytic disease of the newborn (erythroblastosis fetalis)
      ii. ABO incompatibility (almost all are type O mother and either type A or B baby): most common reason for hemolysis in the newborn
      iii. Minor blood group incompatibility (Kell is very antigenic; Kell negative mother), uncommon
    - **Non-immune mediated:** same as above but Coombs is negative; need to see blood smear
      i. Smear shows **characteristic-looking RBCs**: membrane defect (most are either spherocytosis or elliptocytosis)
      ii. Smear shows **normal-looking RBCs**: enzyme defect (most are G6PD deficiency then pyruvate kinase deficiency)
      iii. Extravascular: excessive bruising, cephalohematoma
- Bilirubin is then bound to albumin and carried in the blood; bilirubin may be uncoupled from albumin in the bloodstream to yield free bilirubin, e.g. neonatal sepsis, certain drugs (ceftriaxone), hypoxia, acidosis.
- Bilirubin is transported to the hepatocytes: within the hepatocytes is the conversion of unconjugated (laboratory indirect-acting) fat-soluble bilirubin to conjugated (glucuronide) water-soluble bilirubin (laboratory direct-acting) by the action of **hepatic glucuronyl transferase (GT)**.
  - Decreased enzymatic activity of GT
    - Normal newborn first week of life
    - Primary liver disease of systemic disease affecting the liver (sepsis, TORCH, metabolic diseases)
    - No GT activity: Crigler-Najjar syndrome (type I)

- Transport through the intrahepatic biliary system to the porta hepatis for excretion into the duodenum; abnormalities of transport and excretion cause a conjugated (direct) hyperbilirubinemia (**>2 mg/dL direct-acting bilirubin in the blood in the newborn**).
  - **Biliary atresia** (progressive obliterative cholangiopathy): obstruction at birth due to fibrosis and atresia of the extrahepatic ducts (and so no gall bladder); then variable severity and speed of inflammation and fibrosis of the intrahepatic system which ultimately leads to cirrhosis
    - Most present in first 2 weeks of life with jaundice (conjugated hyperbilirubinemia), poor feeding, vomiting, lethargy, hepatosplenomegaly, **persistent acholic stools and dark urine**
    - **Best initial test:** U/S (triangular fibrotic cord at porta hepatis; no evidence of normal ductal anatomy; no gallbladder)
    - **Most accurate test** (next step): percutaneous liver biopsy (is pathognomonic for this process)
    - **Best initial treatment** (palliative): hepatic portojejunostomy (Kasai procedure)
    - **Best long-term management:** liver transplant
  - Liver disease (primary or secondary to systemic disease): cholestasis (sepsis, perinatal infections, metabolic disease, neonatal hepatitis, severe hypothyroidism and others)
- Intestinal transport and excretion: most bilirubin is eliminated in the stool with final products synthesized with help of colonic bacteria; some bilirubin is eliminated in the urine, some is reprocessed in the liver due to enterohepatic circulation (along with bile acids); **intestinal beta-glucuronidase** hydrolyzes glucuronide-bilirubin bonds to yield some unconjugated bilirubin, which is absorbed into the portal circulation and transported back to the liver to be acted upon by hepatic glucuronyl transferase
  - **Increased enterohepatic circulation**
    - Intestinal obstruction
    - Decreased colonic bacteria (first week of life, prolonged antibiotics, severe diarrhea)
    - Breastfeeding jaundice (due to decreased intestinal peristalsis)
    - Breast-milk jaundice (due to excessive concentration of glucuronidase in breast milk)

Clinical Recall

Which of the following is not a cause of hyperbilirubinemia?

A. Increased red blood cell production

B. ABO incompatibility

C. Biliary atresia

D. Increased activity of hepatic glucuronyl transferase

E. Decreased enterohepatic circulation

Answer: D

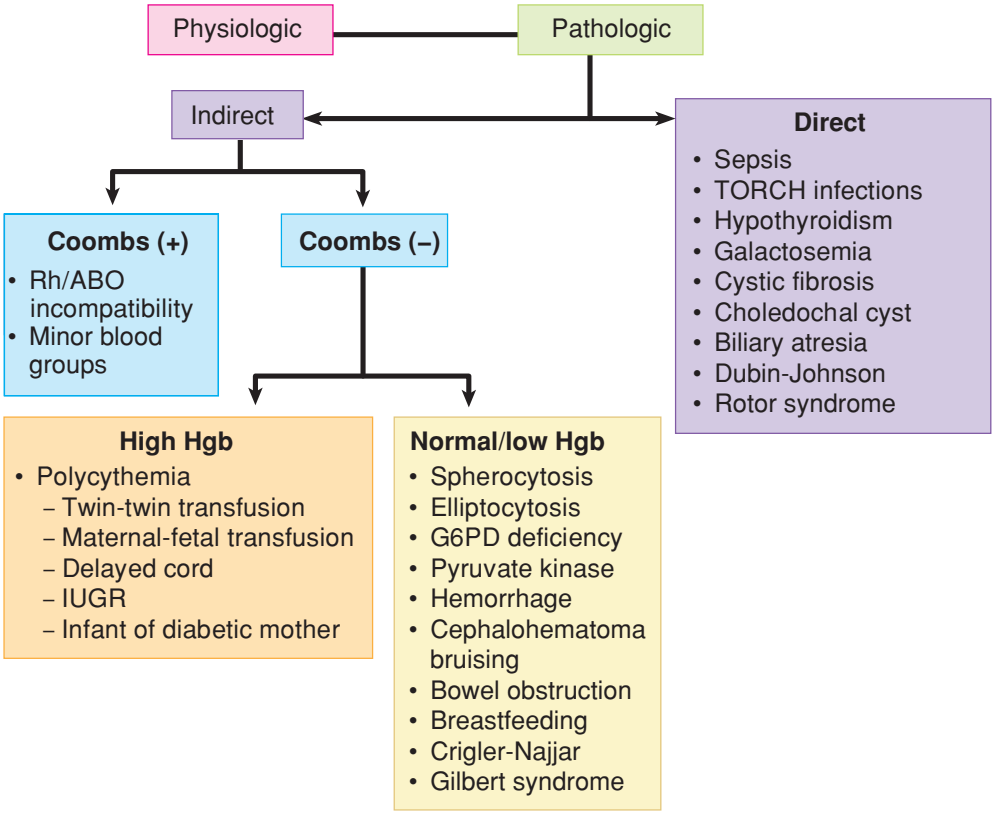

Figure 1-2. Jaundice Workup

Breastfeeding Jaundice Versus Breast-Milk Jaundice

Breastfeeding jaundice means a baby is not getting enough calories through nursing. It occurs in the first few days of life and is common in first-time breastfeeding mothers. While the infant may become dehydrated, lack of calories is what causes the jaundice. In the absence of food in the intestines, peristalsis decreases significantly, allowing much more time for intestinal beta-glucuronidase to hydrolyze the glucuronide bonds and produce more unconjugated (indirect-acting) bilirubin. This enters the portal circulation and is transported back to the liver for further action by hepatic glucuronyl transferase. The result is increased unconjugated bilirubin and increased enterohepatic circulation. Treatment is to obtain a lactation consultation and rehydrate the baby.

Breast-milk jaundice (week 2 of life) is caused by increased glucuronidase in breast milk. More glucuronides are hydrolyzed in the intestine, producing more indirect bilirubin and again increasing enterohepatic circulation. The problem is temporary, because the activity of this enzyme decreases steadily over the first 2–3 months of life and then ceases. Treatment is phototherapy if needed. Bilirubin may rise again, but not to the previous level. The baby may then be safely breastfed.

- Treatment of hyperbilirubinemia
  - Phototherapy
    - Complications: loose stools, erythematous macular rash, overheating leading to dehydration, and **bronze baby syndrome (occurs with direct hyperbilirubinemia; dark, grayish-brown discoloration of the skin** [photo-induced change in porphyrins, which are present in cholestatic jaundice])
  - Double volume exchange transfusion—if bilirubin continues to rise despite intensive phototherapy and/or kernicterus is a concern

Table 1-7. Hyperbilirubinemia and Jaundice

Etiology	Reason for increased bilirubin	Hyperbilirubinemia	Hgb, Hct/ Reticulocytes	Other labs	Treatment
Excessive bruising/ cephalohematoma	RBCs → Hgb → Bilirubin	**In**direct	• Normal to slightly low Hgb/Hct • Normal to slight increase in reticulocytes		Phototherapy
Immune hemolysis • Rh • ABO • Minor blood groups	Anti-Rh, anti-A, anti-B, anti-minor blood group Abs	**In**direct	• Low Hgb/Hct (anemia) • Increased reticulocytes	• Rh negative mother and Rh positive baby • Type O mother and type A or B baby • Direct Coombs positive • Decreased RBCs	Phototherapy + possible exchange transfusion
Polycythemia	High Hct, Hgb → high bilirubin	**In**direct	High (Hct >65)/ normal	Increased RBCs	Phototherapy + partial exchange transfusion
Non-immune hemolysis	Abnormal RBC → splenic removal	**In**direct	Low (anemia)/ increased	• If no membrane defect →, G6PD, PK activity • Characteristic RBCs if membrane defect • Decreased RBCs	Phototherapy + transfusion
Displacement of bound bilirubin from albumin	Free bilirubin in circulation	**In**direct	Normal		Treat underlying problem
Familial nonhemolytic hyperbilirubinemia (Crigler-Najjar syndrome)	Absence of glucuronyl transferase (type I) vs. small amount of inducible GT (type II)	**In**direct	Normal	GT activity	Phototherapy + exchange transfusion
Extrahepatic obstruction—biliary atresia	Bilirubin cannot leave the biliary system	Direct	Normal	Ultrasound, liver biopsy	Portojejunostomy, then later liver transplant
Cholestasis (TORCH, sepsis, metabolic, endocrine)	Abnormal hepatic function → decrease bilirubin excretion	Direct	Normal	With H and P, other select labs suggestive of underlying etiology	Treat underlying problem

Table 1-7. Hyperbilirubinemia and Jaundice (*Cont'd*)

Etiology	Reason for increased bilirubin	Hyperbilirubinemia	Hgb, Hct/ Reticulocytes	Other labs	Treatment
Bowel obstruction	Increased enterohepatic recirculation	**In**direct	Normal		Relieve obstruction + phototherapy
Breastfeeding jaundice	Increased enterohepatic recirculation	**In**direct	Normal		Phototherapy + hydration + teach breastfeeding
Breast milk jaundice	Increased enterohepatic recirculation	**In**direct	Normal		Phototherapy + continued breastfeeding

INFECTIONS

Neonatal Sepsis

A 3-week-old infant presents with irritability, poor feeding, temperature of 38.9 C (102 F), and grunting. Physical examination reveals a bulging fontanel, delayed capillary refill, and grunting.

- Signs and symptoms are very nonspecific.
- Risk factors
  - Prematurity
  - Chorioamnionitis
  - Intrapartum fever
  - Prolonged rupture of membranes
- **Early onset:** first week of life; maternal factors
  - Chorioamnionitis
  - Organisms: group B *Streptococcus, E. coli, Listeria monocytogenes*
- **Late onset:** second week through end of neonatal period; hospital or community-acquired organisms (if still hospitalized: iatrogenic infection)
  - Most common organism: **coagulase negative *S. aureus* (epidermidis)**
- **Diagnosis—**sepsis workup: CBC, differential and platelets, blood culture, urine analysis and culture, chest x-ray; lumbar puncture only for neonates with severe signs (lethargy, hypothermia, hypotonia, poor perfusion, apnea, abnormal neurological findings, or clinical deterioration from birth)
- **Treatment**
  - **If no evidence of meningitis: ampicillin and aminoglycoside until 48–72-hour cultures are negative**
  - **If meningitis or diagnosis is possible: ampicillin and third-generation cephalosporin (*not* ceftriaxone)**

Note

In recent years studies have proven that in the first year of life, lumbar puncture reveals almost no cases of meningitis. Therefore, lumbar puncture should be reserved only for neonates with severe signs.

Note

Toxoplasmosis

Other (syphilis, varicella, HIV, and parvovirus B19)

Rubella

Cytomegalovirus (CMV)

Herpes

Transplacental Intrauterine Infections (TORCH)

TORCH infections are typically acquired in first or second trimester. Most infants have IUGR.

Toxoplasmosis

Toxoplasmosis is a maternal infection worldwide, due primarily to ingestion of undercooked or raw meat containing tissue cysts. Ingestion of water or food with oocytes that have been excreted by infected cats (fecal contamination) is the most common form of transmission in the United States. Advise pregnant women not to change/clean cat litter while pregnant.

- Findings
  - Jaundice, hepatosplenomegaly
  - Thrombocytopenia, anemia
  - Microcephaly
  - **Chorioretinitis**
  - **Hydrocephalus**
  - **Intracranial calcifications**
  - Seizures
- Outcomes
  - Psychomotor retardation
  - Seizure disorder
  - **Visual impairments**
- **Treatment—maternal treatment during pregnancy reduces the likelihood of transmission significantly (spiramycin)**
  - Infants are treated with pyrimethamine, sulfadiazine, and leucovorin.

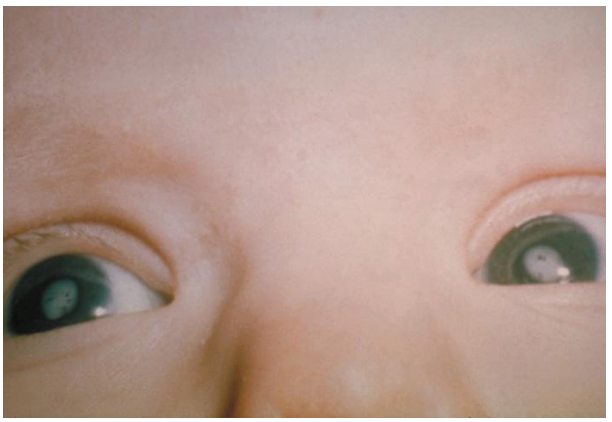

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Figure 1-3. Congenital Cataract Secondary to Maternal Rubella Infection

Congenital rubella

- Classic findings when maternal infection occurs in first 8 weeks' gestation.
- Findings
  - **Blueberry muffin spots** (extramedullary hematopoiesis), thrombocytopenia
  - Cardiac—**PDA, peripheral pulmonary artery stenosis**
  - Eye—**cataracts**
  - **Congenital hearing loss**
  - Thrombocytopenia
  - Hepatosplenomegaly
- Outcomes
  - Hearing loss
  - Persistent growth retardation
  - Microcephaly
  - Mental and motor retardation

Cytomegalovirus (CMV)

- Primary infection (higher risk of severe disease) or reactivation of CMV
- Findings
  - Hepatosplenomegaly, jaundice
  - **Periventricular calcifications**
  - **Intrauterine growth retardation**
  - Chorioretinitis
  - **Microcephaly**
  - Thrombocytopenia, hemolytic anemia
- Outcomes
  - **Sensorineural hearing loss**
  - Neuromuscular abnormalities
  - **Intellectual disability**

Herpes simplex

- Keratoconjunctivitis, skin (5–14 days), CNS (3–4 weeks), disseminated (5–7 days)
- Best diagnosis: PCR, any body fluid
- Best treatment: IV acyclovir ASAP
- Outcomes
  - Microcephaly, spasticity
  - Deafness
  - Blindness
  - Seizure disorder
  - Psychomotor retardation
  - Death
- **Prevention is elective Cesarean section when active disease or visible lesions are identified; however, this is not 100% effective.**
- **Treatment—acyclovir**

Congenital syphilis

- Transplacental transmission usually during second half of gestation
- **At-risk infants must undergo serologic testing at the time of delivery.**
- Findings
  - Early (birth–2 yrs): snuffles, maculopapular rash (including palms of soles, desquamates), jaundice, periostitis, osteochondritis, chorioretinitis, congenital nephrosis
  - Late (>2 years of age): Hutchinson teeth, Clutton joints, saber shins, saddle nose, osteochondritis, rhagades (thickening and fissures of corners of mouth)
- **Diagnosis—*Treponema* in scrapings (most accurate test) from any lesion or fluid, serologic tests**
  - Infant with positive VDRL plus pathognomonic signs; if not, perform serial determinations—increasing titer in infection
  - **Most helpful specific test is IgM-FTA-ABS** (immunoglobin fluorescent treponemal antibody absorption) but it is not always positive immediately.
- **Treatment—penicillin**

Varicella

- Neonatal
  - Seen when delivery occurs <1 week before/after maternal infection
  - Treat with VZIG (varicella zoster immune globulin), if mother develops varicella 5 days before to 2 days after delivery.
- Congenital
  - Associated with limb malformations and deformations, cutaneous scars, microcephaly, chorioretinitis, cataracts, and cortical atrophy
  - Associated with infection during 1st or 2nd trimester

Many of the findings of the **TORCH infections** are very similar, so note the most likely presentations:

- Toxoplasmosis: hydrocephalus with **generalized calcifications** and chorioretinitis
- Rubella: the classic findings of **cataracts, deafness, and heart defects**
- CMV: microcephaly with **periventricular calcifications**; petechiae with thrombocytopenia; hepatosplenomegaly; sensorineural hearing loss
- Herpes: skin vesicles, keratoconjunctivitis, acute meningoencephalitis
- Syphilis: osteochondritis and periostitis; skin rash involving palms and soles and is desquamating; **snuffles** (mucopurulent rhinitis)

Clinical Recall

Which of the following TORCH infections is correctly matched to an associated finding?

A. Rubella: patent ductus arteriosus

B. CMV: maculopapular rash

C. Herpes simplex: chorioretinitis

D. Congenital syphilis: periventricular calcifications

E. Varicella: snuffles

Answer: A

Genetics/Dysmorphology 2

Learning Objectives

- ❑ Demonstrate understanding of chromosome abnormalities
- ❑ Solve problems concerning early overgrowth with associated defects, defects with facial features as the major defect, osteochondrodysplasias, and disorders of connective tissue
- ❑ Explain information related to unusual brain and/or neuromuscular findings with associated defects

ABNORMALITIES OF CHROMOSOMES

Trisomy 21 (Down Syndrome)

Down syndrome is the **most common** pattern of human malformation.

- Genetics
  - 94% full trisomy 21(nondisjunction); risk of recurrence 1–2% and then increases with **advancing maternal age**
  - 4–6% with translocation; most are new mutations but must obtain parental karyotypes for possible balanced translocation carrier
- Findings
  - **Upward slanting palpebral fissures; speckling of iris (Brushfield spots); inner epicanthal folds**
  - Small stature, mouth open with tongue protrusion**;** mild microcephaly, short neck, flat occiput, short metacarpals and phalanges; **single palmar crease**
  - **Hypotonia**
  - **Hearing loss (sensorineural, conductive, and mixed)**
  - Primary gonadal deficiency
  - **Cardiac anomaly—ECD > VSD > PDA, ASD; also MVP**
  - GI anomalies: **duodenal atresia, Hirschsprung**
  - **Atlanto-axial instability**
  - **Hypothyroidism**
  - **Acute lymphocytic leukemia** (but acute myeloblastic leukemia if in first 3 years of life)
  - **Intellectual disability, variable**

Cardiac Abbreviations

ASD: atrial septal defect

ECD: endocardial cushion defect

MVP: mitral valve prolapse

PDA: patent ductus arteriosus

VSD: ventricular septal defect

- Natural history
  - Major cause for early mortality is congenital heart disease
  - Muscle tone improves with age
  - Rate of development slows with age
  - Early onset of Alzheimer disease

Trisomy 18 (Edwards Syndrome)

Edwards syndrome is the **second most common** pattern of human malformation.

- Genetics—older maternal age; nondisjunction
- Findings
  - Growth deficiency
  - **Intellectual disability**
  - **Low-set, malformed ears; microcephaly, micrognathia; prominent occiput**
  - **Clenched hand—index over third; fifth over fourth**
  - **Short sternum**
  - **VSD, ASD, PDA, cyanotic lesions**,
  - **Rocker-bottom feet, hammertoe**
  - **Omphalocele**
- Natural history
  - Many spontaneous abortions
  - Feeble from birth
  - Most do not survive first year

Trisomy 13 (Patau Syndrome)

Patau syndrome is a defect of midface, eye, and forebrain development → single defect in first 3 weeks' development of prechordal mesoderm. It involves older maternal age.

- Findings
  - **Holoprosencephaly and other CNS defects**
  - **Severe intellectual disability**
  - **Microcephaly; microphthalmia**
  - **Severe cleft lip, palate, or both**
  - **Scalp defects in parietal-occipital area** (cutis aplasia)
  - **Postaxial polydactyly**
  - VSD, PDA, ASD, cyanotic lesions
  - Single umbilical artery

Aniridia–Wilms Tumor Association (WAGR Syndrome)

- Genetics
  - 1/70 with aniridia also has Wilms
  - WAGR syndrome: deletion of 11p13; **W**ilms + **A**niridia + **G**U anomalies + M**R**
  - Have 45–60% chance of developing Wilms tumor

Klinefelter Syndrome (XXY)

- Genetics; most common findings manifested at puberty
- Findings
  - **Decreased IQ** (average IQ 85–90)
  - **Behavioral/psychiatric problems**
  - **Long limbs** (decreased upper:lower segment ratio)
  - Slim (weight/height ratio low)
  - **Hypogonadism and hypogenitalism** (testosterone replacement at age 11–12 years) = hypergonadotropic hypogonadism (increased FSH and LH, and decreased testosterone)
  - Infertility in almost all
  - Gynecomastia

Turner Syndrome (XO)

- Genetics
  - Generally sporadic; no older maternal age seen
  - Paternal chromosome more likely to be missing
  - Many mosaic patterns (including Y-chromatin)
- Findings
  - Small-stature female
  - Absence of one SHOX gene (short stature homeobox; embryonic regulation of skeletal system, especially arms and legs)
  - Abnormal GH–IGF receptor axis
  - Gonadal dysgenesis–streak ovaries in XO
  - Average IQ 90
  - **Congenital lymphedema, residual puffiness over dorsum of fingers and toes**
  - **Broad chest, wide-spaced nipples**
  - **Low posterior hairline; webbed posterior neck**
  - **Cubitus valgus (elbow) and other joint problems**
  - **Horseshoe kidney and other renal defects**
  - Cardiac:
    - **Bicuspid aortic valve** (number 1 cardiac anomaly)
    - **Coarctation** (Turner syndrome is the condition in which this is seen most often, but it is **not** the most common cardiac condition in Turner syndrome)
    - Aortic stenosis, mitral valve prolapse
    - Hypertension common, even without cardiac or renal disease
  - Primary hypothyroidism, mostly autoimmune, and other autoimmune diseases (celiac disease)
- Natural history
  - Decreased height velocity with delayed bone age
  - **Estrogen treatment indicated**
  - **May increase height by 3–4 cm with growth hormone (GH)**

Note

Gonadal dysgenesis is not evident in childhood, so chromosomes are warranted in any short-stature female whose phenotype is compatible with Turner syndrome.

Also consider in any adolescent with absent breast development by age 13, pubertal arrest, or primary/secondary amenorrhea with increased FSH.

Fragile X Syndrome

- Genetics
  - Fragile site on long arm of X in affected males and some carrier females—Molecular diagnosis—variable number of repeat CGG (preferred diagnosis = DNA-based molecular analysis)
  - With the genetic mutation, can get trinucleotide expansion during meiosis to a premutation state (50-200 repeat CGG); this is passed on to progeny and may then further expand to the full mutation (>200 CGG); then, epigenetic methylation occurs → gene silencing → **protein inactivation** = full syndrome. More likely meiotic expansion in future generations = **genetic anticipation**
  - X-linked dominant—males (most common cause of inherited intellectual disability); due to lyonization (random inactivation of one X), there are generally fewer abnormalities seen in girls but they may present with decreased IQ
  - There is no meiotic expansion in males; can only pass premutation to daughters
  - Males with the full syndrome are infertile
- Findings
  - **Mild to profound intellectual disability; learning problems;** anxiety, depression, and **autistic-like behaviors**
  - **Large ears, dysmorphic facial features, large jaw, long face**
  - **Large testes—mostly in puberty (macroorchidism)(fertile)**
- Natural history—normal lifespan

EARLY OVERGROWTH WITH ASSOCIATED DEFECTS

Beckwith-Wiedemann Syndrome

- Genetics
  - Usually sporadic
  - IGF-2 disrupted at 11p15.5 (imprinted segment); therefore, both copies of the gene are expressed (normally one is silenced), leading to overgrowth
- Findings
  - **Macrosomia**
  - **Macroglossia—may need partial glossectomy**
  - **Pancreatic beta cell hyperplasia—excess islets → hypoglycemia;** hypoglycemia may be refractory; glucose control most important initial management
  - Umbilical abnormalities, diastasis recti, **omphalocele**
  - **Hemihypertrophy** → increased risk of abdominal tumors (Wilms)
- **Management—obtain ultrasounds and serum AFP every 6 months through 6 years of age to look for Wilms tumor and hepatoblastoma**

UNUSUAL BRAIN AND/OR NEUROMUSCULAR FINDINGS WITH ASSOCIATED DEFECTS

Prader-Willi Syndrome

- Genetics
  - Most with deletion at 15q11-q13–imprinted segment
  - **Paternal** chromosome responsible
  - The **same deletion** causes both Prader-Willi and Angelman syndromes. This may be due to the **normal process of imprinting**, which is **epigenetic** (change in the chromatin and not the gene sequence) silencing (due to hypermethylation) of certain genes in either the male or female germ cells. The alleles in the opposite germ line are expressed and therefore in the zygote this results in **monoallelic gene expression** so that for any imprinted segment there is a **functional haploid state**. It is established in the germ line and maintained in all somatic cells.
    - If the deletion occurs in the **male germ cell**, then the inheritance is from the only expressed genes, which are maternal. This is Prader-Willi syndrome.
    - If the deletion occurs in the **female germ cell**, then the inheritance is from the only expressed genes, which are paternal. This is Angelman syndrome.
  - Negligible recurrence risk
- Findings
  - First year, difficulty feeding with poor growth; then, increased feeding and weight gain plus slow height attainment (short stature)
  - **Obesity—onset from 6 months to 6 years**
  - **Mild to severe intellectual disability**
  - **Food-related behavioral problems (binge eating)**
  - **Small hands and feet, puffy; small genitalia**
  - **Hypothalamic-pituitary dysfunction (growth, thyroid, adrenal) hypogonadotropic-hypogonadism;** hypothalamic-pituitary dysfunction other than GH deficiency and hypogonadism is variable
- Natural history—decreased life expectancy relative to morbid obesity

Angelman Syndrome (Happy Puppet Syndrome)

- Genetics—also deletion of 15q11-q13, but **maternally derived** (imprinted segment)
- Findings
  - **Severe MR**
  - **Paroxysms of inappropriate laughter**
  - **Absent speech or <6 words (100%); most can communicate with sign language**
  - **Ataxia and jerky arm movements resembling a puppet's movements (100%)**
  - Seizures—most at age 4 years, may stop by age 10

OSTEOCHONDRODYSPLASIAS

Achondroplasia/Hypochondroplasia

- Genetics: autosomal dominant; most common short-limb dwarfism; 90% from new gene mutation; older paternal age; mutations in gene for fibroblast growth factor receptor 3 at 4p16.3 (*FGFR3*)
- Findings
  - **Short stature (increased upper-to-lower segment ratio; short-limbed dwarfism)**
  - **Proximal femur shortening**
  - **Megalocephaly, small foramen magnum (may have hydrocephalus), small cranial base, prominent forehead**
  - **Lumbar lordosis**
- Natural history
  - Normal intelligence
  - Spinal cord compression is rare (cervicomedullary junction); usually occurs in first year of life
  - Tendency of late childhood obesity
  - Small eustachian tube—otitis media and hearing loss
  - Early cervical compression, respiratory problems, obstructive and central apnea, later cardiovascular disease

CONNECTIVE TISSUE DISORDERS

Marfan Syndrome

- Genetics: autosomal dominant with wide variability; mutation in fibrillin gene (*FBN1*)—15q21.1
- Findings
  - Early rapid growth of the appendicular skeleton and anterior ribs
  - Major findings are skeletal, cardiovascular, and ocular
  - **Tall stature with long, slim limbs and little fat**
  - Arm span > height
  - **Arachnodactyly**
  - Decreased U:L segment ratio (as with XXY)
  - **Joint laxity with kyphoscoliosis**
  - Pectus excavatum or carinatum
  - **Lens subluxation (upward; defect in suspensory ligament)**; secondary glaucoma, myopia, retinal detachment
  - **Ascending aortic dilatation with or without dissecting aneurysm** (uncommon in children and adolescents unless case is severe) with secondary aortic regurgitation. Mitral valve disease (MVP and regurgitation) is the most common in children.
- Natural history
  - Prevent scoliosis
  - Vascular complications chief cause of death
  - Evaluate heart and aorta

Ehlers-Danlos Syndrome

- Genetics: type I most common (now 6 types); autosomal dominant with wide variability
- Findings
  - **Droopy ears**
  - **Hyperextensible skin, fragile, easy bruisability, poor wound healing**
  - **Joint hyperlaxity; tendency toward hip, shoulder, knee, and clavicular dislocation**
  - MVP, tricuspid valve prolapse, **aortic root dilatation;** dissecting aneurysm, ASD
  - **Blue sclera**, myopia, glaucoma, **ectopia lentis**, retinal detachment
  - Intracranial aneurysm

Note

Ehlers Danlos patients tend to have thin sclerae, allowing the darker underlying choroid to shine through with a blue-gray tinge.

Osteoporosis in Children

Osteomalacia is undermineralization of normal bone volume, while **osteoporosis** is normal mineralization but a decrease in bone volume, especially trabecular (vertebral). By definition, with osteoporosis there is also osteopenia, a decreased amount of total bone tissue). It is associated with pathological (atraumatic) fractures.

- **Primary osteoporosis**: heritable connective tissue disorders
- **Secondary osteoporosis:** neuromuscular disorders, chronic illness, endocrine disorders, drug-induced, inborn errors of metabolism

Table 2-1. Primary Osteoporosis in Children

Disease	Defect	Genetics	Comment
Osteogenesis imperfecta	Structural or quantitative defect of type I collagen, the primary component of the extracellular matrix of bone and skin	• Autosomal dominant: all racial and ethnic groups • Autosomal recessive: ethnic groups with consanguinity	Most common genetic cause of osteoporosis
Ehlers-Danlos syndrome	Quantitative deficiency of fibrillar collagen (collagen molecules packed together to form long, thin fibrils)	Four autosomal dominant types and 2 autosomal recessive	One AD type, vascular has decreased longevity
Marfan syndrome	Mutations in the gene (FBN1) encoding for the extracellular matrix protein fibrillin-1, the major constituent of microfibrils	Autosomal dominant	Mostly skeletal, ocular and cardiovascular findings
Homocystinuria	Classic form: cystathionine-β-synthase deficiency: increase of both methionine and homocysteine in body fluids and decrease to absence of plasma cystine	Autosomal recessive	Phenotype similar to Marfan syndrome but some differences
Polyostotic fibrous dysplasia (McCune-Albright syndrome)	Postzygotic activating mutation causing overproduction of endocrine protein products independent from normal feedback control; precocious puberty with polyostotic fibrous dysplasia and café-au-lait spots	Noninherited; 2x more in girls	Other endocrinopathies due to overproduction (pituitary, thyroid, adrenal)

ENVIRONMENTAL AGENTS

Table 2-2. Environmental Agents

Embryopathy	Major Findings	Comments
Fetal alcohol	• **Neurobehavioral and developmental abnormalities** (in worst cases, intellectual disability) • **Mid-face dysmorphism** (from abnormal frontal lobe development): short palpebral fissures, maxillary hypoplasia, short and smooth philtrum and indistinct philtrum-vermillion border • **Pre and postnatal growth deficiency:** symmetric IUGR then short stature, slow growth, and acquired microcephaly • PLUS in worse cases: cardiac and joint anomalies	Most common teratogen; may not have a maternal history, so must make diagnosis by first 3 listed findings
Fetal hydantoin	IUGR, hypertelorism; flat, broad nasal bridge and hypertelorism, short nose, cleft lip and palate, malformed ears, web neck, **hirsutism, congenital heart disease**	Similar features with carbamazepine, primidone and phenobarbital; no dose-response relationship
Fetal valproate	**Neural tube defects, prominent metopic ridge**, cleft lip and palate, radial defects, hypospadias, congenital heart disease, **absence of first rib**	
Fetal warfarin	Nasal hypoplasia, microphthalmia, microcephaly, **Dandy-Walker malformation**, intellectual disability, scoliosis, congenital heart disease	
Retinoic acid	**Affects neural crest and branchial arch development: microtia, anotia**; hypertelorism, flat, depressed nasal bridge, intellectual disability, learning problems, **conotruncal anomalies**	• All treated females must take a pregnancy test, use definitive method of birth control plus 1 back-up method, receive counseling about teratogenicity; no problems if stopped prior to 15th postmenstrual day • Also obtain baseline liver tests and lipid panel

Clinical Recall

A newborn girl found to be small for gestational age has wide-spaced eyes, increased body hair, and a ventricular septal defect on echocardiography. What was she most likely exposed to in utero?

A. Valproic acid

B. Phenytoin

C. Warfarin

D. Retinoic acid

E. Alcohol

Answer: B

MISCELLANEOUS CONDITIONS

Potter Sequence

- Etiology
  - **Renal agenesis/dysgenesis** or other type of urinary tract defect must occur prior to 31 days' gestation → **oligohydramnios** (also from chronic leakage)
  - Leads to **fetal compression (mid-face, ears)**
  - Lack of alveolar sac development → **pulmonary hypoplasia**
- Findings
  - **Pulmonary hypoplasia**
  - **Potter facies**—hypertelorism, epicanthal folds, low-set flattened ears, micrognathia, compressed flat nose
  - Breech presentation
  - Abnormal positioning of hands and feet; deformations, limb anomalies
  - **Death from respiratory insufficiency (hypoplasia)**

VACTERL Association

- Nonrandom association of

  V = Vertebral defects

  A = Anal atresia (imperforate anus)

  C = Cardiac defects (VSD and others)

  T = TE fistula

  E = Esophageal atresia

  R = Renal defects

  L = Limb defects (radial)

CHARGE Syndrome

Most cases now known to be caused by a mutation in CHD7 gene (8q12.2), which provides instructions for making a protein that regulates chromatin remodeling. When this is the cause, it follows autosomal dominant inheritance; a small number have no known cause or inheritance pattern.

- Nonrandom association of

  C = Coloboma (from isolated iris to anophthalmos; retinal most common)

  H = Heart defects (TOF, PDA, and others)

  A = Atresia choanae

  R = Retardation of growth and/or development

  G = Genital hypoplasia (in males)

  E = Ear anomalies and/or deafness

Note

U/S is necessary for the parents/siblings of patients with oligohydramnios secondary to agenesis and/or dysgenesis of both kidneys. This is because 9% of first-degree relatives have asymptomatic malformations.

Growth and Nutrition 3

Learning Objectives

- ❑ Demonstrate steps in evaluation of growth
- ❑ Solve problems related to breastfeeding, feeding of solids, and other feeding issues
- ❑ Answer questions related to growth disorders

CHILDHOOD GROWTH

Basic Principles of Growth

In the **first week of life**, a newborn typically loses up to **10% of birth weight** (**BW**) due to the elimination of large amounts of extravascular fluid. By **2 weeks**, BW should be regained or surpassed. In the **first month of** life, a neonate should gain ~30 grams (1 oz) per day, which slows to ~20 grams/day at 3–4 months.

- By **6 months**, an infant typically doubles BW, and by **1 year**, triples BW.
- Growth rate slows further between 6 and 12 months and then appetite begins to decline through 18 months of age.
- Then height and weight increase at a steady rate, but head-circumference rate of growth decreases somewhat (2–5 years).
- Between age 6 and 12 years: **3–6 growth spurts** each year for 8-week periods each; slower brain growth; **myelination complete by age 7**
- Between age 10 and 20 years: acceleration in early adolescence. Boys' highest growth stops at age 18. **Their average peak is 13.5 years (2–3 years later than girls, and continues 2–3 years after girls have stopped).** Girls' **average peak is 11.5 years and it stops at age 16.**

Assessment of Growth

- A child is genetically programmed to stay on 1–2 growth curves after age 2 years.
- The height percentile at age 2 years correlates with final adult height percentile.
- Low-birth-weight and very-low-birth-weight infants may continue to show **catch-up growth through early school age.**
- **Weight/height <5th percentile is the single best growth curve indicator for acute malnutrition.** In nutritional insufficiency, weight decreases before length, and weight/height

is low. For causes of decreased linear growth, length decreases first or at the same time as weight (e.g., GH deficiency).

- **Body mass index (BMI) is accepted as best clinical indicator for measure of under- and overweight.**
- For bone age-reference standards, use **radiographs of left hand and wrist. Skeletal maturity is linked more to sexual maturity than chronologic age.**

Growth Patterns

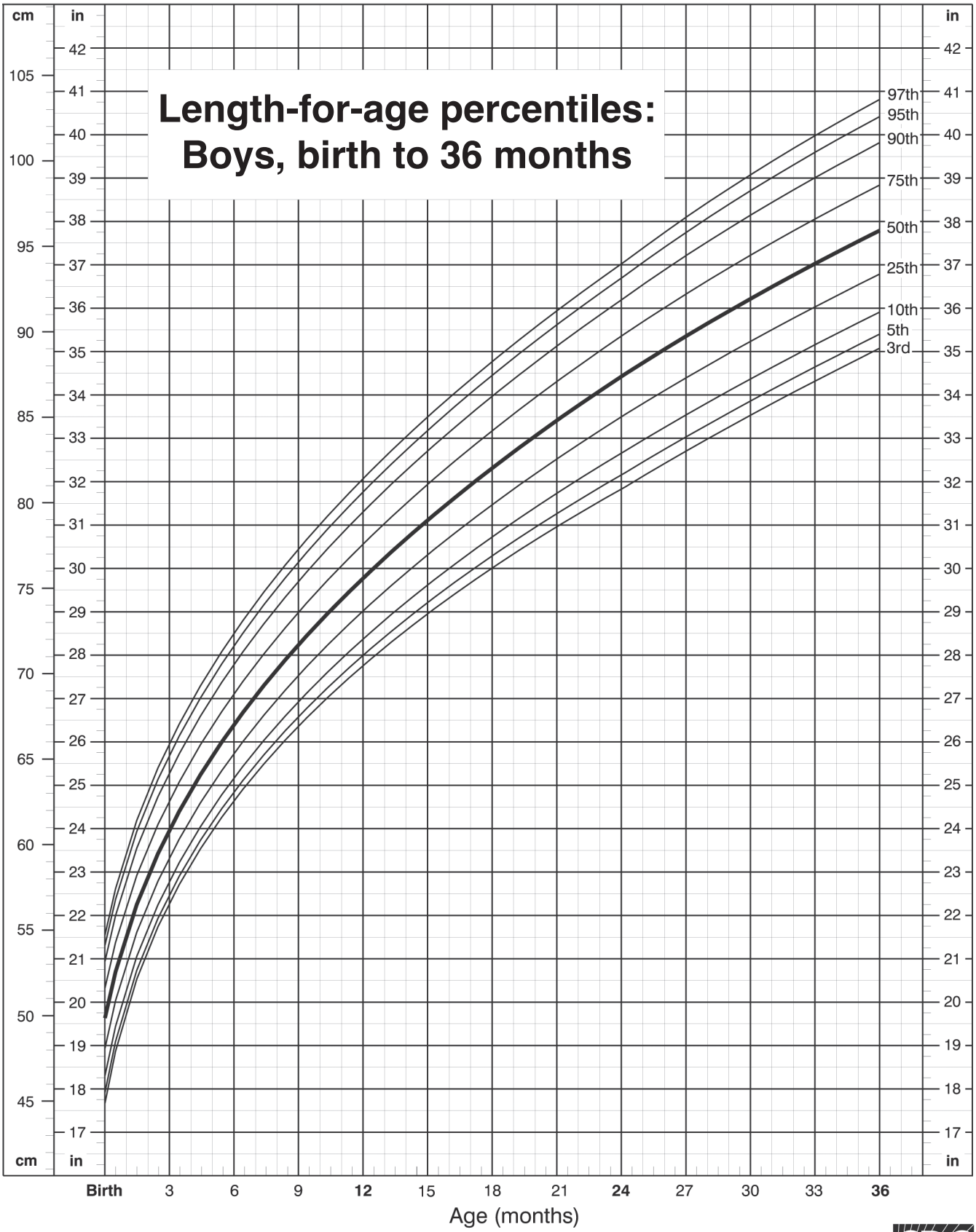
The **growth chart is the best tool to determine patterns of growth,** with separate charts for boys and girls. The **charts measure weight for age, height for age, head circumference for age, weight for height, and BMI.** Each chart has multiple curves (either 5–95% or 3–97%).

Evaluation of Growth

- **Growth velocity**: yearly increments of growth; should follow a growth curve

$$\text{slope} = \frac{\text{change in height}}{\text{change in age}}$$

- **Chronologic age (CA)**: actual age
- **Bone age (BA)**: x-ray of left hand and wrist (non-dominant hand)



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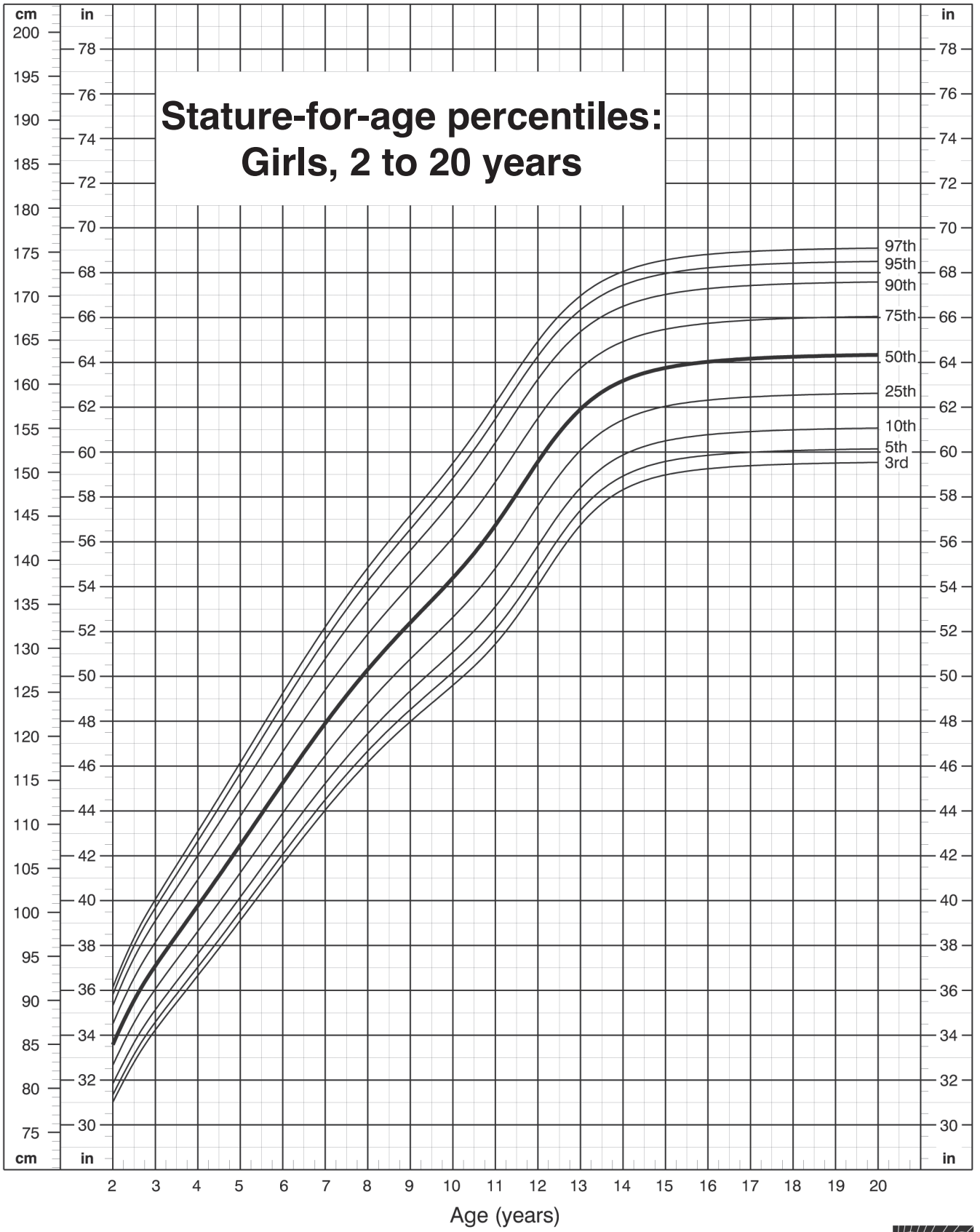

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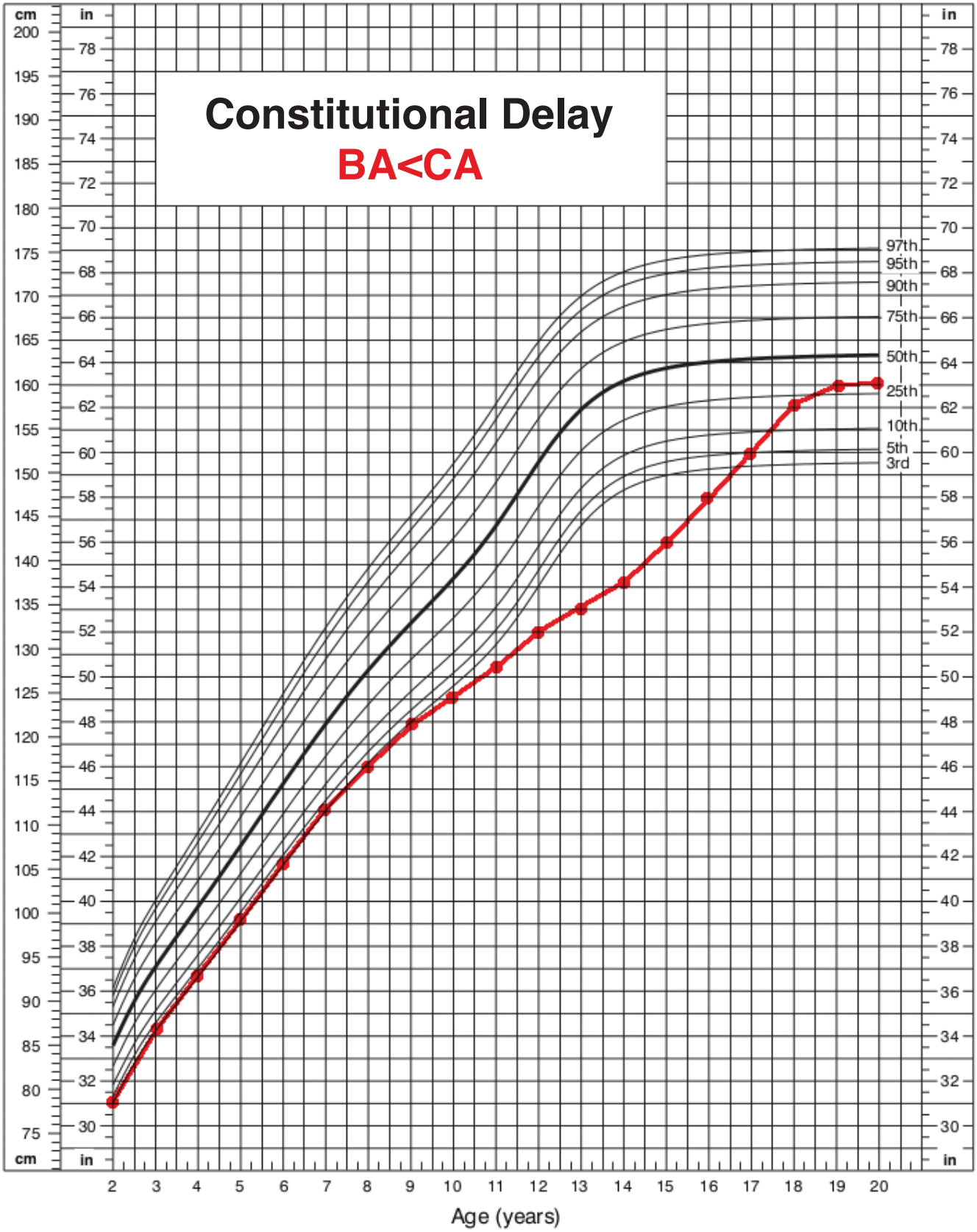

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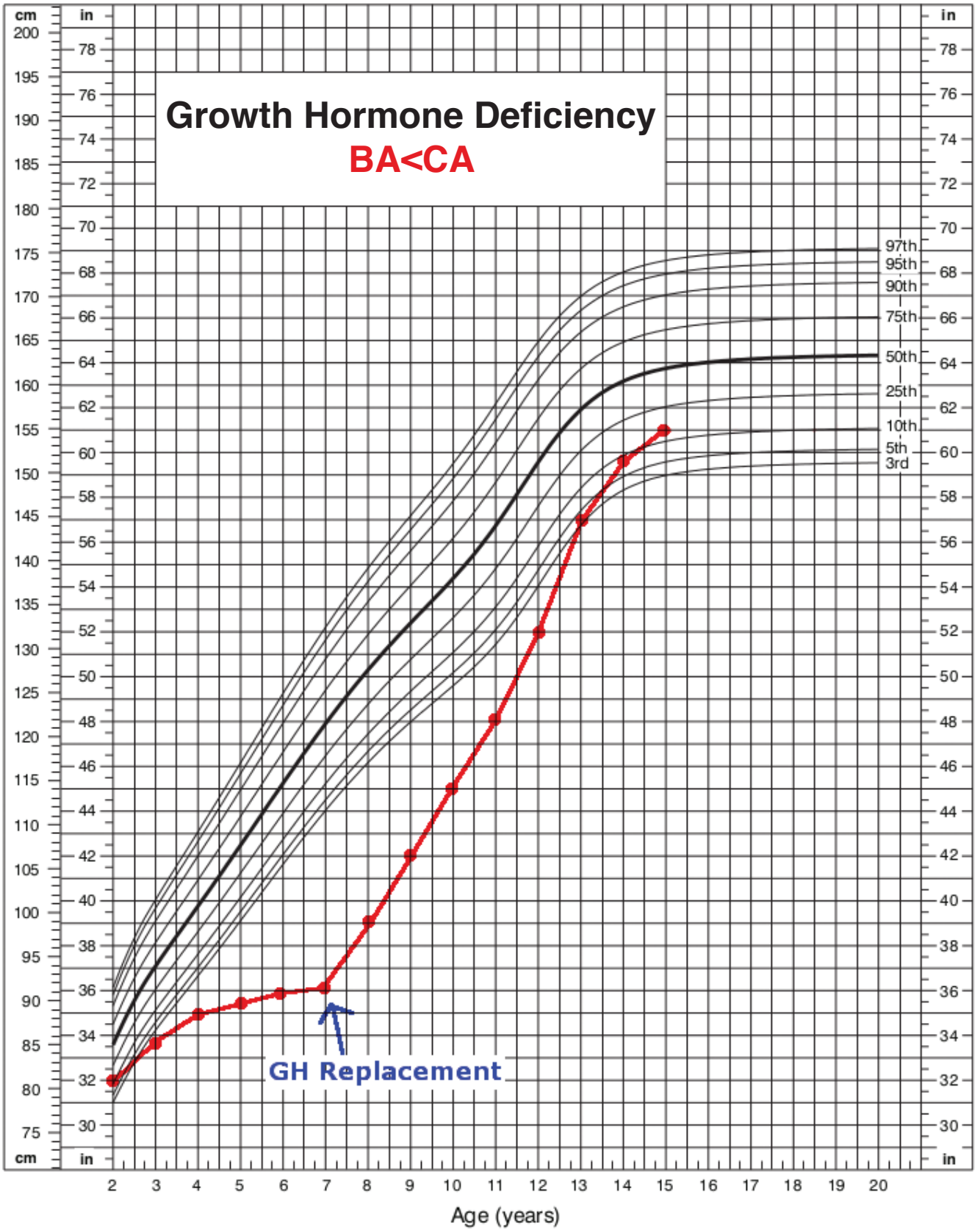

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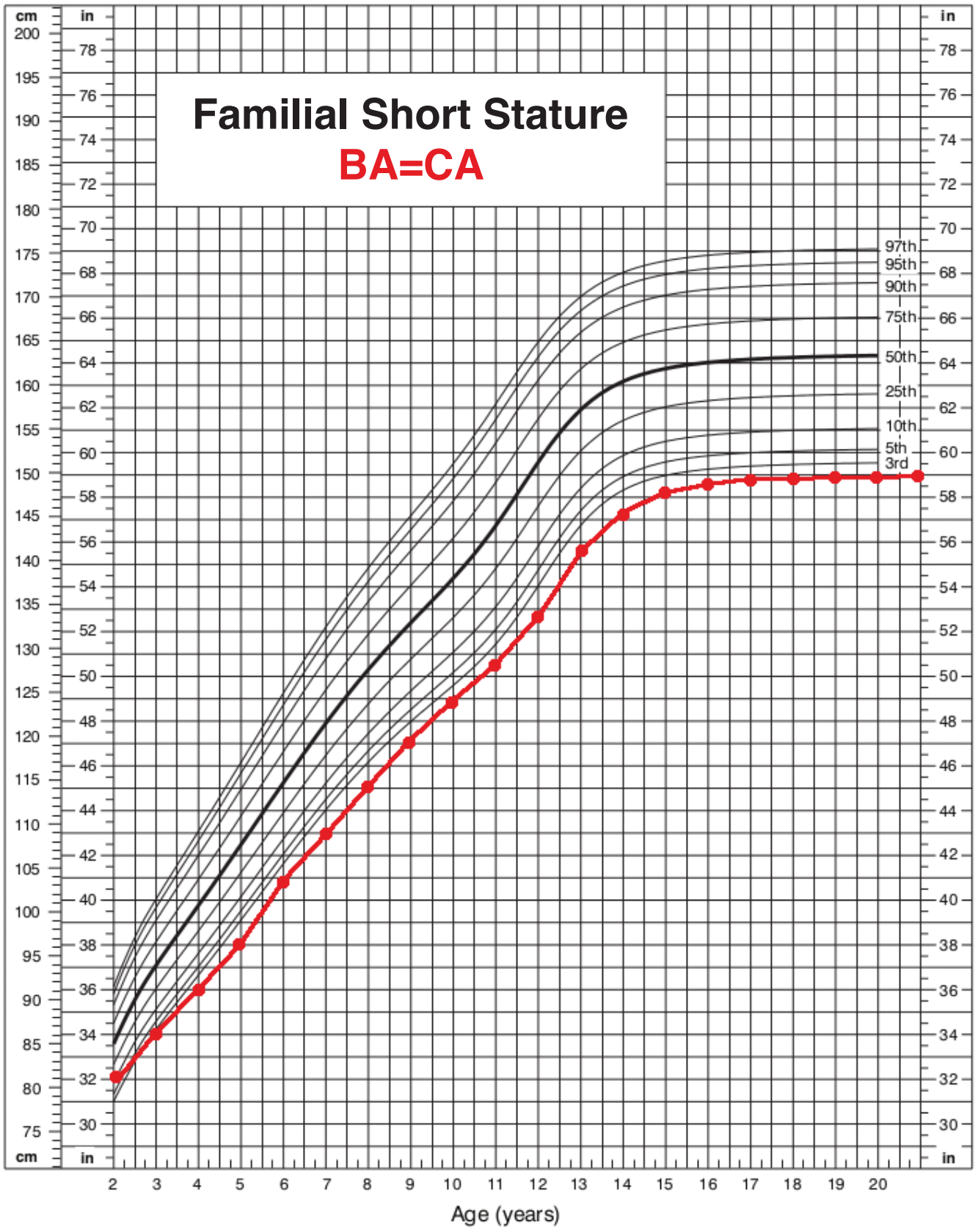


Adapted from CDC.gov/National Center for Health Statistics

DISORDERS OF GROWTH

Note

Suspect *Turner syndrome* in females with pathologic short stature.

Suspect *craniopharyngioma* if short stature and vision problems.

Height

Short stature

A father is worried that his 13-year-old son is short. The child has been very healthy. He is below the 5th percentile for height and has been all his life. Physical exam is normal. Father is 6 foot 3; mother is 5 foot 10. Father was a "late bloomer."

- Constitutional growth delay—child is short prior to onset of delayed adolescent growth spurt; parents are of normal height; normal final adult height is reached; growth spurt and puberty are delayed; bone age delayed compared to chronological age.
- Familial short stature—patient is parallel to growth curve; strong family history of short stature; chronologic age equals bone age.
- Pathologic short stature—patient may start out in normal range but then starts crossing growth percentiles. Differential diagnosis: craniopharyngioma, hypothyroidism, hypopituitarism, nutritional problems, and other chronic illnesses.

Table 3-1. Growth Velocity

	Normal	Abnormal
Bone age = chronological age	Ideal Genetic (familial) **short stature**	• Genetic • Chromosomal
Bone age < chronological age	Constitutional delay	• Chronic systemic disease • Endocrine related
Bone age ≥ chronological age	Obesity (tall) Familial **tall stature**	• Precocious puberty • Congenital adrenal hyperplasia • Hyperthyroidism

Tall stature

- Usually a normal variant (familial tall stature)
- Other causes—exogenous obesity, endocrine causes (growth hormone excess [gigantism, acromegaly], androgen excess [tall as children, short as adults])
- Syndromes—homocystinuria, Sotos, Klinefelter

Weight

Organic failure to thrive

A baby weighs 16 pounds at 1 year of age. Birth weight was 8 pounds. He has irritability, diarrhea, and abdominal distension. He was doing well until age 9 months when he started to eat the food that the rest of the family eats. His length curve is just starting to flatten.

- Causes include malnutrition, malabsorption (infection, celiac disease, cystic fibrosis, disaccharide deficiency, protein-losing enteropathy), allergies, immunodeficiency, and chronic disease
- Initial diagnostic tests (when organic causes are suspected)—**document caloric intake,** CBC, urinalysis, liver function tests, serum protein, **sweat chloride**, stool for ova and parasites

Clinical Recall

An 8-year-old boy has been under the 2nd percentile for height all of his life. Hand x-ray for bone age assessment reveals a bone age of 8 years. Which of the following is the most likely diagnosis?

A. Hypothyroidism

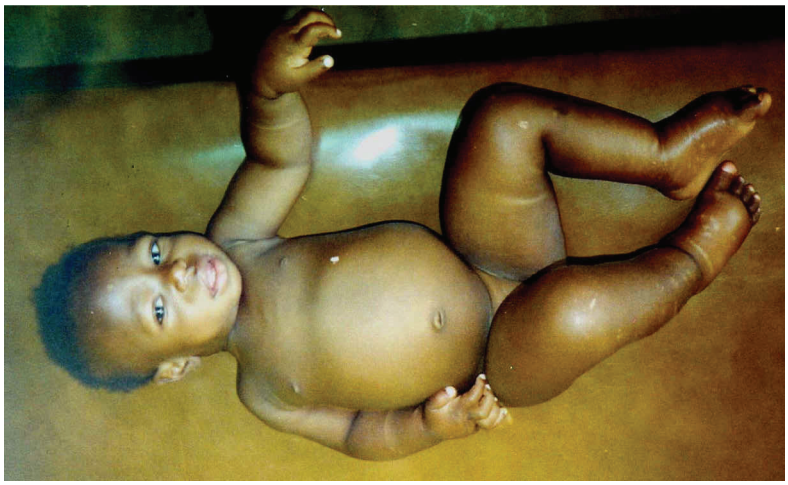
B. Constitutional growth delay

C. Familial short stature

D. Chronic illness

E. Poor nutritional status

Answer: C



Courtesy of Tom D. Thacher, M.D.

Figure 3-1. Kwashiorkor

Note generalized edema secondary to low serum albumin.

Non-organic failure to thrive

A 4-month-old infant presents to the emergency department because of upper respiratory symptoms. The patient is <5th percentile in weight and length. He is 3.5 kg. Birth weight was 4.2 kg. The mother states that the child takes 16 oz of infant formula per day with cereal added. Physical exam reveals a baby with little subcutaneous fat, long dirty fingernails, impetigo, and a flat occiput.

- Emotional or maternal deprivation plus nutritional deprivation leads to neglect (psychosocial deprivation); also look at socioeconomic and intelligence issues of parents
- Clinically, children are thin and wasted-appearing and may have poor hygiene; developmental delays, social delays (no eye contact, no expression); feeding aversion
- Major emphasis of diagnosis is not on medical testing but on showing that child can gain appropriate weight with good care (may need hospitalization)
- Report all cases with respect to maternal neglect to Child Protective Services (CPS); require long-term intervention

Obesity

- Risk factors—predisposition, parental obesity, family/patient inactivity, feeding baby as response to any crying, and rarely associated in syndromes (Prader-Willi; Down)
- Presentation—tall stature in some, abdominal striae, associated obesity of extremities; increased adipose tissue in mammary tissue in boys, large pubic fat pad, early puberty
- Diagnostic tests—BMI >85% signifies overweight to obese
- Complications—Obese infants and children are at increased risk of becoming obese adults (the risk is greater with advanced age of onset); cardiovascular (hypertension, increased cholesterol), hyperinsulinism, slipped capital femoral epithesis, sleep apnea, type 2 diabetes, acanthosis nigricans.
- Treatment—exercise and balanced diet; **no medications**

FEEDING

A normal newborn has sufficient stores of iron to meet requirements for 4–6 months, but iron stores and absorption are variable. Breast milk has less iron than most formula, but has higher bioavailability.

- Formula is supplemented with vitamin D; breastfed infants must be supplemented from birth (400 IU/d)
- Vitamin K is routinely given intramuscularly at birth, so no supplementation needed
- Both breast milk and formula are 90% H_2O, so no additional H_2O needed

Breastfeeding

A nursing mother asks if her 3-month-old baby requires any vitamin supplementation.

Most infants can breastfeed immediately after birth and all can feed by 4–6 months. The feeding schedule should be by self-regulation; most establish by 1 month.

- Advantages
  - Psychological/emotional—maternal-infant bonding
  - Premixed; right temperature and concentration
  - Immunity—**protective effects** against enteric and other pathogens; **less diarrhea, intestinal bleeding, spitting up, early unexplained infant crying, atopic dermatitis, allergy, and chronic illnesses** later in life; passive transfer of T-cell immunity
  - Decreased allergies compared to formula fed
  - Maternal—weight loss and faster return to preconceptional uterine size
- Contraindications: HIV; HBV; CMV; HSV (if lesions on breast); acute maternal disease if infant has no disease eg, tuberculosis, sepsis; breast cancer; substance abuse
  - Drugs: (**absolute contraindications**) antineoplastics, radiopharmaceuticals, ergot alkaloids, iodide/mercurials, atropine, lithium, chloramphenicol, cyclosporin, nicotine, alcohol
  - Drugs (**relative contraindications**) neuroleptics, sedatives, tranquilizers, metronidazole, tetracycline, sulfonamides, steroids
  - **No contraindication with mastitis**

Clinical Recall

For which of the following new mothers may breastfeeding be recommended?

A. A woman with HIV

B. A woman with mastitis

C. A woman taking lithium for bipolar disorder

D. A woman with breast cancer on chemotherapy

E. A woman suspected to be using drugs of abuse

Answer: B

Note

Mothers with HBV infection are free to breastfeed **after** the neonate has received the appropriate recommended vaccinations against HBV.

Table 3-2. Breast Milk Versus Cow Milk

Component	Human Milk	Cow Milk
Water/solids	Same	Same
Calories	20 cal/oz	20 cal/oz
Protein	1–1.5% (whey dominant)	3.3% (casein dominant)
Carbohydrate	6.5–7% lactose	4.5% lactose
Fat	high in low chain fatty acids	high in medium chain fatty acids
Minerals	Iron better absorbed	Low iron and copper
Vitamins	Diet dependent, low in K	Low in C, D
Digestibility	Faster emptying	Same after 45 days
Renal solute load	Low (aids in renal function)	Higher

Formula Feeding

Note

Do not give cow milk to infants age <1.

- **Infant formulas.** Formula feeding is used to **substitute** or **supplement** breast milk. Most commercial formulas are cow-milk–based with modifications to approximate breast milk. They contain **20 calories/ounce**. Specialty formulas (soy, lactose-free, premature, elemental) are modified to meet specific needs.
- Cow milk (whole milk) should not be introduced until after the full first year of life. Introduction of **cow milk <1 yr promotes iron-deficiency anemia** (low Fe in cow milk plus low bioavailability; also causes erosion of GI mucosa, leads to blood loss and therefore Fe loss).
- Advanced feeding—Stepwise addition of foods (one new food every 3–4 days)

SOLIDS

- Iron-fortified cereal only at 4-6 months (when infant is developmentally able to take cereal by spoon)
- Step-wise introduction of strained foods (vegetables and fruits), then dairy, meats (6-9 months; stage I pureed and stage II chunkier)
- Table foods at 9-12 months
- No honey in first year of life—infant botulism

Development 4

Learning Objective

❑ Explain information related to primitive reflexes and developmental milestones

OVERVIEW

Development includes 5 main skill areas: visual-motor, language, motor, social, and adaptive.

- Assessment is based on acquisition of milestones occurring sequentially and at a specific rate: each skill area has a spectrum of normal and abnormal
  - abnormal development in one area increases likelihood of abnormality in another area, **so careful assessment of all skills** is needed
  - developmental diagnosis is a functional description/classification and does not specify an etiology
- Developmental delay is performance significantly below average, i.e., developmental quotient (developmental age/chronologic age × 100) of <75; may be in ≥1 areas; 2 assessments over time are more predictive than a single assessment
- Major developmental disorders
  - Intellectual disability: **IQ <70–75 *plus* related limitation in ≥2 adaptive skills**, e.g., self-care, home living, work, communication
  - Communication disorders (deficits of comprehension, interpretation, production, or use of language)
  - Learning disabilities, one or more of (defined by federal government; based on standardized tests): reading, listening, speaking, writing, math
  - Cerebral palsy
  - Attention deficit/hyperactivity disorder
  - Autism spectrum disorders

Developmental Evaluation

- Thorough history and physical
- Developmental testing—age-appropriate motor, visual, cognitive, language, behavioral and learning
- Denver II Developmental Assessment
  - Tool for screening the apparently normal child between ages 0–6
  - Suggested at every well-child care visit
  - Allows generalist to identify possible delay → need further evaluation for definitive diagnosis
  - Screens in gross motor, fine motor, language, personal-social
  - **For infants born <38 weeks' gestation, correct age for prematurity up to age 2 years**
  - Failure is at least 2 delays

PRIMITIVE REFLEXES AND DEVELOPMENTAL MILESTONES

An infant can sit up with its back straight, has started crawling, has a pincer grasp, and plays peek-a-boo. What age is most appropriate for this baby?

- Appear and disappear in sequence during specific periods of development
- **Absence or persistence beyond a given time frame signifies CNS dysfunction**

Included here are the major milestones indicative of specific ages. Exam questions typically describe an infant's/child's skills and ask for the corresponding age.

Table 4-1. Newborn Reflexes

Reflex	Description	Appears	Disappears	CNS Origin
Moro	Extend head → extension, flexion of arms, legs	Birth	4–6 mo	Brain stem vestibular nuclei
Grasp	Finger in palm → hand, elbow, shoulder flexion	Birth	4–6 mo	Brain stem vestibular nuclei
Rooting	Cheek stimulus → turns mouth to that side	Birth	4–6 mo	Brain stem trigeminal system
Trunk incurvation	Withdrawal from stroking along ventral surface	Birth	6–9 mo	Spinal cord
Placing	Steps up when dorsum of foot stimulated	Birth	4–6 mo	Cerebral cortex
Asymmetric tonic neck (ATNR)	Fencing posture when supine	Birth to 1 month	4–6 mo	Brain stem vestibular nuclei
Parachute	Simulate fall → extends arms	6–8 mo	Never	Brain stem vestibular

Table 4-2. Developmental Milestones

	Gross Motor	Visual Motor	Language	Social Adaptive
Birth	• Symmetric movements in supine • Head flat in prone	• Visually fixes on an object	• Alerts to sound	• Regards face
2 months	• Head in midline while held sitting • Raises head in prone • Begins to lift chest	• Follows past midline	• Smiles in response to touch and voice	• Recognizes parent
4 months	• Holds head steadily • Supports on forearms in prone • Rolls from prone to supine	• Reaches with both arms together • Hands to midline	• Laughs • Orients to voice • Coos	• Likes to look around
6 months	• Sits with support (tripod) • Feet in mouth in supine	• Unilateral reach • Raking grasp • Transfers object	• Babbles	• Recognizes that someone is a stranger
7 months	• Rolls from supine to prone • May crawl • Starts to sit without support			
9 months	• Crawls well • Pulls to stand • Starting to cruise	• Immature pincer grasp • Holds bottle • Throws object (not overhand)	• "Mama," "dada," indiscriminately • Understands "no" • Understands gestures	• Plays gesture games • Explores environment (crawling and cruising)
12 months	• May walk alone (must by 18 months)	• Mature pincer grasp • Crayon marks • Object permanence (from 10 months)	• 1-2 words other than "mama" and "dada" (used appropriately) • Follows 1-step command with gesture	• Imitates actions • Comes when called • Cooperates with dressing
15 months	• Creeps up stairs • Walks backward	• Scribbles and builds towers of 2 blocks in imitation	• 4-6 words • Follows 1-step command without gesture	• Uses cup and spoon (variable until 18 months)
18 months	• Runs • Throws objects overhand while standing	• Scribbles spontaneously • Builds tower of 3 blocks	• 15-25 words • Knows 5 body parts	• Imitates parents in tasks • Plays in company of other children

(*Continued*)

Table 4-2. Developmental Milestones (*Cont'd*)

	Gross Motor	Visual Motor	Language	Social Adaptive
24 months	• Walks up and down stairs one foot at a time	• Imitates stroke (up or down) with pencil • Builds tower of 7 blocks • Removes clothing	• 50 words • 2-word sentences • Follows 2-step commands • Uses pronouns inappropriately	• Parallel play
3 years	• Alternates feet going up the stairs • Pedals tricycle	• Copies a circle • Undresses completely • Dresses partially • Unbuttons • Dries hands	• ≥250 words • 3-word sentences • Plurals • All pronouns	• Group play • Shares • Takes turns • Knows full name, age and gender
4 years	• Alternates feet going downstairs • Hops and skips	• Copies a square • Buttons clothing • Dresses completely • Catches ball	• Knows colors • Recites songs from memory • Asks questions	• Plays cooperatively • Tells "tall tales"
5 years	• Skips alternating feet • Jumps over lower obstacles	• Copies triangle • Ties shoes • Spreads with knife	• Prints first name • Asks what a word means • Answers all "wh-" questions • Tells a story • Plays pretend • Knows alphabet	• Plays cooperative games • Abides by rules • Likes to help in household tasks

Clinical Recall

A young boy is able to walk and build a tower with 7 blocks. He plays well alongside other children and can say "my toy" or "my turn," with an inventory of about 50 words. What is the most likely age of the child?

A. 12 months

B. 15 months

C. 18 months

D. 24 months

E. 36 months

Answer: D

Possible Abnormalities

You must take into account the number of weeks of prematurity to assess development appropriately, i.e., per the preterm age, NOT chronological. For instance, a 6-month-old baby born at 32 weeks (i.e., 2 months preterm) must be assessed at 6 – 2 = 4 months CORRECTED AGE. Do this until chronological age 2 years, then consider delays to be true.

- If there appears to be a language delay, first consider conductive hearing loss. While all babies receive hearing testing within the first month of life, that is for congenital sensorineural hearing loss. Over the first year of life, conductive hearing loss may occur from repeated ear infections.
- If there is a lack of development or regression of language skills with impaired social interaction, restricted activities and interests and stereotypic behaviors, consider autistic spectrum disorder. Onset of abnormal findings must occur age <3 years.
  - After a complete H and P with neurologic exam and development testing, the first step is to perform an autism screening questionnaire. If you feel the diagnosis is likely, the next step is to refer to a specialist in this area.
- Delay is defined as ≥1 **skills significantly below average**, i.e., developmental quotient (developmental age/chronological age x 100) is <75. When you find this, you must first look for a possible reason, and the child will need developmental therapy in ≥1 areas.

Behavioral/Psychological Disorders 5

Learning Objective

- ❑ Solve problems concerning eating disorders, elimination disorders, and sleep disorders

EATING DISORDERS

Pica

- Repeated or chronic ingestion of non-nutritive substances, e.g., paint, dirt
- After year 2, needs investigation
- Predisposing factors
  - **Intellectual disability and lack of parental nurturing**
  - Also with family disorganization, poor supervision, and psychologic neglect
- More common with autism, brain-behavior disorders, and **low socioeconomic status**
- Increased risk for **lead poisoning, iron deficiency, and parasitic infections**

ELIMINATION DISORDERS

Enuresis

A 7-year-old boy has problems with bedwetting. The mother says that during the day he has no problems but is usually wet 6 of 7 mornings. He does not report dysuria or frequency, and has not had increased thirst. The mother also says that he is a deep sleeper.

- Voluntary or involuntary repeated discharge of urine after a developmental age when bladder control should be present (most by age of **5 years**); there are 2 types
- **Primary:**
  - **No significant dry period**; most common and usually **nocturnal** (nocturnal enuresis)
  - Hyposecretion of ADH and/or receptor dysfunction

  - Relationship of sleep architecture, diminished arousability during sleep, and abnormal bladder function; anatomic malformations
  - Management—thorough history and physical, (should begin with behavioral treatment; not definitive, varying success rates):
    - Enlist cooperation of child—chart dryness, reward system
    - Child should void before going to sleep
    - Alarm to wake once 2–3 hours after falling asleep; may use alarm that goes off when child wets a special sheet (bell and pad alarm)
    - No punishment or humiliation
    - Psychotherapy for traumatized children or when behavioral therapy has failed
    - Pharmacotherapy for failed behavioral therapy in nocturnal enuresis—oral desmopressin (DDAVP)
- **Secondary**:
  - **After a period of dryness ≥6 months**
  - Causes—psychological, urinary tract infection, constipation, diabetes
  - More common in girls
  - Evaluation—urinalysis
  - Management—treat underlying disorder
- **Children with both diurnal and nocturnal enuresis:**
  - Especially with voiding difficulties, more likely to have abnormalities of the urinary tract
  - Ultrasonography or flow studies are indicated in these cases.

Encopresis

- Passage of feces into inappropriate places after a chronologic age of 4 years, or equivalent developmental level
- May be primary or secondary
- Causes—psychological (toilet phobia), early toilet training, aggressive management of constipation, painful defecation, fissures
- Types
  - Retentive encopresis most common:
    - 2/3 of cases
    - **Hard stool on rectal examination is sufficient to document, but a negative exam requires a plain abdominal x-ray**
    - Presence of fecal retention is evidence of chronic constipation, and thus treatment will require **active constipation management**
    - May have abnormal anal sphincter function
- Associations
  - Primary encopresis—especially in boys, associated with global developmental delays and enuresis
  - Secondary encopresis—high levels of psychosocial stressors and conduct disorder

- Management
  - **Clear impacted fecal material (with mineral oil or laxative)** but avoid long-term laxative use
  - Concomitant behavioral management
  - Regular postprandial toilet-sitting
  - High-fiber diet
  - Familial support for behavior modification
  - Group or individual psychotherapy

Clinical Recall

A concerned mother brings her 4-year-old son to the physician for evaluation of nocturnal enuresis. The boy has never had a significant dry period. He has regular bowel movements without constipation or encopresis. What is the most appropriate next step?

A. Encourage the mother to use a bell and pad alarm system

B. Order a urinalysis to assess for infection

C. Punish the child whenever he wets the bed

D. Refer the mother and child to psychotherapy

E. Reassure the mother that this is normal for the boy's age

Answer: E

SLEEP DISORDERS

Parasomnias

Parasomnias are **episodic** nocturnal behaviors that often involve cognitive disorientation and autonomic and skeletal muscle disturbance

- Associated with relative CNS immaturity
- More common in children than adults; abate with age

Table 5-1. Parasomnias

Sleepwalking and Sleep Terrors (Partial Arousal)	Nightmares
• First third of night	• Last third of night
• During slow-wave sleep	• REM sleep
• **No daytime sleepiness or recall**	• **Daytime sleepiness** (if prolonged waking) and **vivid recall**
• High arousal threshold (agitated if • awakened)	• **Low arousal threshold** (easily awakened)
• **Common family history**	• No family history
• Displaced from bed	• May be displaced from bed
• Sleepwalking relatively common; night terrors rare	• Very common
• Treatment: parental education, **reassurance**, avoid exacerbating factors, i.e., sleep deprivation, **safety precaution**s	• No required treatment unless persistent/ frequent, in which case possible abuse or anxiety disorder should be investigated.

Immunizations 6

Learning Objectives

- ❑ Define active immunization
- ❑ Describe different routes of immunization for specific routine vaccines

A 6-month-old patient is being seen for routine care. The baby is doing well, and physical examination, growth, and development are normal. The mother states that after the last set of immunizations the baby had a temperature of 39.4 C (103 F) and cried for 2 hours but was consolable. What is your advice to this mother before administering the next set of immunizations?

ACTIVE IMMUNIZATIONS

Table 6-1. Classification of Vaccines

Live Attenuated		
	• Viral	MMR, varicella, yellow fever, nasal influenza, smallpox, oral rotavirus
	• Bacterial	BCG, oral typhoid
Inactivated		
Whole	• Virus	Polio, rabies, hepatitis A
Fractional	• Protein-based	Subunit: hepatitis B, parenteral influenza, acellular pertussis
	• Polysaccharide based	Toxoid: diphtheria, tetanus
		Pure: pneumococcal, Hib, meningococcal
		Conjugate: Hib, pneumococcal, meningococcal

Vaccine Rules

For stimulation of an adequate and persisting antibody response, 2 or more doses are usually required. In general, vaccines from different manufacturers are interchangeable.

- Most vaccines can be safely and effectively administered simultaneously.
- **A lapse in schedule does not require reinstitution of the entire series.**
- Unknown or uncertain immunization status
  - **When in doubt, the child should be considered to be disease-susceptible, and appropriate immunizations should be initiated without delay.**
  - **To be counted, the vaccine(s) must be documented on a formal immunization record, regardless of country.**
- Dose—No reduced dose or divided dose should be administered, **including to babies born prematurely or at low birth weight (exception: first dose hepatitis B).**
- Active immunization of people who recently received gamma globulin
  - **Live virus vaccine may have diminished immunogenicity when given shortly before or during the several months after receipt of immunoglobulin (Ig) so live vaccine is delayed (3–11 months).**

Institute of Medicine Immunization Safety Review Committee findings

- Available evidence **does not support the hypothesis that the MMR causes autism, associated disorders, or inflammatory bowel disease.** (Lancet report of Wakefield has been found to be fraudulent)
- Based on epidemiologic evidence, there is **no causal relationship between multiple immunizations and increased risk of immune dysfunction and type 1 diabetes.**
- There is no causal relationship between hepatitis B vaccine administration and demyelinating neurologic disorders.
- There is no causal relationship between meningococcal vaccination and Guillain-Barré.
- Preservative thimerosal (Hg-containing) not causative of any problems (has now been removed)

Misconceptions

The following are *not* contraindications to immunizations:

- A reaction to a previous DTaP of temperature <40.6 C (<105 F), redness, soreness, and swelling
- A mild, acute illness in an otherwise well child
- Concurrent antimicrobial therapy
- Prematurity—immunize at the chronological age
- A family history of seizures
- A family history of sudden infant death syndrome

Accepted Precautions and Contraindications

- Minor illness, with or without a fever, **does not contraindicate immunization.**
- **Fever, per se, is not a contraindication.**
  - **Guidelines for administration are based on the physician's assessment of illness and on specific vaccines the child is scheduled to receive.**
  - If fever or other problems suggest moderate or serious illness, the child should not be immunized until recovered.

Live Vaccines and Immune Status

- No live vaccines with primary B-cell defects, except for selective IgA deficiency
- May be given with **incomplete** DiGeorge syndrome (if CD3 count >500 and CD8 >200 and there are normal mitogen responses)
- May give live viral vaccines but not **bacterial** (oral typhoid, BCG) with phagocytic defects
- May give live vaccines with complement defects
- HIV: may give rotavirus, MMR, and varicella if health status related to HIV conditions is good and CD4% >15%; otherwise they are delayed
- Chemotherapy: MMR and varicella can be given ≥3 mos after completion of therapy except for anti B-cell drugs, where longer periods may be necessary (e.g. rituximab, ≥6 mos)

ACTIVE IMMUNIZATION AFTER DISEASE EXPOSURE

Measles

Table 6-2. Measles

Age	Management (post-exposure)
0–6 months	Immune serum globulin if mother is not immune
Pregnant or immunocompromised	Immune serum globulin
All others	Vaccine within 72 hours of exposure for susceptible individuals

Varicella

- Give vaccine **to susceptible immunocompetent contacts age >12 months as soon as possible and VZIG to all immunocompromised and susceptible pregnant women.** No vaccine or VZIG for healthy infants age 0-12 months.
- **VZIG also for** susceptible pregnant women, **newborn whose mother had the onset of chickenpox within 5 days before delivery to 48 hours after delivery,** and certain hospitalized premature infants

Hepatitis

- Hepatitis B: after exposure in nonimmune patient, give hepatitis B Ig plus vaccine; repeat vaccine at 1 and 6 months.
- Hepatitis A: if patient is not vaccinated, give 1 dose of vaccine as soon as possible but within 2 weeks of exposure

Mumps and Rubella

- Not protected by postexposure administration of live vaccine
- Recommended for exposed adults who were born in the United States in or since 1957 and who have not previously had or been immunized against either; except pregnancy

SPECIFIC VACCINES (ROUTINE VACCINATION)

Hepatitis B

- First dose should be given soon after birth, before hospital discharge, with a total of **3 doses by age 18 months** if mother is HBsAg negative.
- **The infant born to a hepatitis B surface antigen (HBsAg)-positive mother should receive the first dose of hepatitis B virus (HBV) plus hepatitis B Ig at 2 different sites within 12 hours of birth;** all 3 doses should be given by age 6 months (treat same as exposure).
- All children and adolescents who have not been immunized should begin the series during any visit to the physician.

DTaP

- All DTaP vaccines for the United States currently contain acellular **pertussis**.
- The rates of local reactions, fever, and other common systemic reactions are **substantially lower with acellular pertussis vaccines than with whole-cell vaccine (but may still occur).** Use DT if there has been a serious reaction. No full dose pertussis or diphtheria after age 7 years, 0 days.
- Total of 5 doses is recommended before school entry, with the final given at **preschool age, 4–6 years.**
- Pertussis booster (Tdap) vaccine **is now recommended during adolescence, regardless of immunization status; is also recommended even if one has already had pertussis disease.**
- Tdap (childhood tetanus) is given at **age 11–12**, and then Td (adult tetanus) every 10 years; may be given any time after 7th birthday if needed because it contains only partial doses of diphtheria and pertussis

Tetanus

Table 6-3. Tetanus Prophylaxis in Wound Management

History of Doses of Tetanus Toxoid	Clean, Minor Wounds		All Others*	
	Td	TIG	Td	TIG
<3 or unknown	Yes	No	Yes	Yes
≥3	No, unless >10 years from last dose	No	No, unless >5 years from last dose	No

Definition of abbreviations: TIG, tetanus immune globulin; Td, tetanus and diphtheria vaccine.

*All other wounds = increased risk of tetanus: dirt, saliva, feces, avulsions, frostbite, puncture, crush, burns, and missiles.

IPV

- Inactivated is now the **only poliovirus vaccine available in the United States**.
- Four doses of IPV, with the last at **preschool age, 4–6 years**
- Any child up to 18 years of age should receive all doses, if behind.
- Any child who has received OPV from another country should complete schedule in United States with IPV.

HiB Conjugated Vaccine

- ***Does not* cover nontypeable *Haemophilus***
- Depending on the vaccine brand, the recommended primary series consists of 3 or 4 doses.
- After the primary series, an additional booster dose is recommended at 12–15 months of age, regardless of which regimen was used for the primary series.
- If immunization is not initiated (i.e., child is behind) **until age 15–59 months**, then there is catch-up (1 dose), but **not given after age 5 years in normal children**
- Invasive disease does not confirm immunity; patients still require vaccines if age appropriate, i.e., age <5 years.

Pneumococcal Vaccines

- Pneumococcal conjugate vaccine (PCV13)
  - Purified polysaccharides of 13 serotypes conjugated to diphtheria protein
  - Routine administration as a **4-dose series for all children age 15 months and younger**
  - If no dose given yet between age 15–59 months, then there are catch-up doses
- 23-valent pneumococcal polysaccharide vaccine (PS23)—**given as additional protection to the PCV13 in some high-risk children (e.g., functional/anatomic asplenia) age >2 years**
- Age ≥65 years (PPSV-23)

Varicella

- Recommended at **age 12 months or older for healthy people who have not had varicella illness, with second dose at age 4–6 years**
- **Catch-up dosing:** both doses should be given for proper immunity
- May still have breakthrough varicella; milder than unimmunized, rarely spreads
- Has been associated with the development of herpes zoster after immunization (rare)
- Most people age >18 years, even without a reliable history of varicella infection, will still be immune.

MMR

- Live attenuated vaccine: issues are similar to those for varicella
- First dose given at **age 12–15 months**
- Second dose given at **preschool age, 4–6 years**
- Catch-up with 2 doses
- **Documented egg allergy is *not* a contraindication to the MMR.** MMR is derived from chick embryo fibroblast tissue cultures but *does not* contain significant amounts of egg cross-reacting proteins.
- HIV: varicella and MMR should be given if CD4 showing >15 CD4/total lymphocytes AND no AIDS-related illness at vaccination time
- Immunoglobulin-containing products: if given recently, must wait to administer varicella and MMR, as IG may inactivate the live vaccine

Note

Advantages of conjugated polysaccharide vaccines (HIB, PCV13, MCV4) over nonconjugated:

- Effective <2 years of age
- Effect from booster doses
- Long-term immunity

Hepatitis A Vaccine

- Recommended for all children age >1 year **(12–23 months)**
- **Two doses, 6 months apart**
- Also recommended routinely for chronic liver disease patients, homosexual and bisexual men, users of illegal drugs, patients with clotting-factor disorders, and those at risk of occupational exposure
- Can give with other vaccines

Meningococcal Conjugate Vaccine (MCV4)

Administer MCV4 to

- All children at **the age 11–12 visit and booster at age 16**
- **All college freshmen living in dormitories, if not vaccinated**
- There is now a vaccine for **serotype B** for high risk patients and during outbreaks (status post concurrent type B outbreaks at Princeton and UC Santa Barbara)
- Meningococcal B vaccine is recommended only for those at increased risk for meningococcal B disease—persistent complement component deficiencies (C3, C5-C9, properdin, factor D, factor H); anatomic or functional asplenia, including sickle cell disease; and those residing in a community with a serogroup B meningococcal disease outbreak per the local health department on the basis of CDC criteria (college students not considered at increased risk since the incidence is not greater than that of the same-aged general population)

Note

MPSV4 is the older, pure polysaccharide vaccine, while MCV4 is the newer, conjugated vaccine.

Influenza Vaccine

- Inactivated influenza vaccine (typical flu shot)
  - Administered intramuscularly
  - Inactivated influenza vaccine has been deemed safe in egg-allergic patients
  - Given annually during flu season for children age >6 months (A strains, B strains, and H_1N_1)
- Live influenza vaccine
  - Live attenuated vaccine has recently had only 3% effectiveness so has not been used in last 2 seasons; the AAP has stated that it may be used in 2019 season, but the preferred vaccine is the quadrivalent inactivated vaccine
- **Influenza vaccine** contains egg protein but studies have shown that, like reactions secondary to any component in any vaccine, there are only **rare instances of severe reaction** in people who truly have an egg protein allergy. As a result, the American Academy of Pediatrics states that children with egg allergy can receive influenza vaccine with **no additional precautions** than those considered for any vaccine. This means that for **any** vaccine administration, the patient should be observed post-administration and any severe allergic manifestations should be anticipated and treated appropriately with medication should they occur.

Rotavirus Vaccine

- Oral live attenuated vaccine
- Given at ages 2, 4, 6 months
- Essentially no catch-up if behind (no dose after age 8 months)
- Older vaccine was associated with cases of intussusception; current vaccine is reformulated and there are few cases. Intussusception precludes getting another dose.

Human Papillomavirus (HPV) Vaccine

- Quadrivalent vaccine (6, 11, 16, 18) or bivalent vaccine (16, 18) to girls at the age 11-12 visit (through age 26) for cervical cancer prevention
- Quadrivalent vaccine (6, 11, 16, 18) to boys age 11–12; for genital warts caused by HPV 6,11.
- Can give in both males and females as early as age 9.
- 3 doses
  - Now 9-valent in both girls (9–26) and boys (9–15): 6, 11 (genital warts), 16, 18, 31, 33, 45, 52, 58 (cervical cancer prevention)
  - Precancerous lesions (all 9) including anal intraepithelial neoplasia
  - Anal cancer (16, 18, 31, 33, 45, 52, 58)
- Doses 2 and 3: give at 2 months and then 6 months after first

Clinical Recall

An 11-year-old girl is brought to the emergency department after falling off her bicycle on a trail in the forest. She has a few minor wounds, some of which contain dirt or tree debris. Her primary vaccines were completed at age 5 and she has not no vaccines since that time. What treatment should she receive?

A. Tetanus and diphtheria (Td) vaccine only

B. Td vaccine + tetanus immune globulin (TIG)

C. TIG only

D. Diphtheria vaccine only

E. Tetanus vaccine only

Answer: A

For more details and specific footnotes, go to cdc.gov/vaccines.

Table 1 Recommended Child and Adolescent Immunization Schedule for ages 18 years or younger, United States, 2020

These recommendations must be read with the notes that follow. For those who fall behind or start late, provide catch-up vaccination at the earliest opportunity as indicated by the green bars. To determine minimum intervals between doses, see the catch-up schedule (Table 2). School entry and adolescent vaccine age groups are shaded in gray.

Vaccine	Birth	1 mo	2 mos	4 mos	6 mos	9 mos	12 mos	15 mos	18 mos	19–23 mos	2–3 yrs	4–6 yrs	7–10 yrs	11–12 yrs	13–15 yrs	16 yrs	17–18 yrs
Hepatitis B (HepB)	1st dose	2nd dose			◄---------- 3rd dose ----------►												
Rotavirus (RV): RV1 (2-dose series), RV5 (3-dose series)			1st dose	2nd dose	See Notes												
Diphtheria, tetanus, acellular pertussis (DTaP <7 yrs)			1st dose	2nd dose	3rd dose			◄---- 4th dose ----►				5th dose					
Haemophilus influenzae type b (Hib)			1st dose	2nd dose	See Notes		◄-- 3rd or 4th dose, See Notes --►										
Pneumococcal conjugate (PCV13)			1st dose	2nd dose	3rd dose		◄---- 4th dose ----►										
Inactivated poliovirus (IPV <18 yrs)			1st dose	2nd dose	◄---------- 3rd dose ----------►							4th dose					
Influenza (IIV)					Annual vaccination 1 or 2 doses								or	Annual vaccination 1 dose only			
or																	
Influenza (LAIV)											Annual vaccination 1 or 2 doses			Annual vaccination 1 dose only			
Measles, mumps, rubella (MMR)					See Notes		◄---- 1st dose ----►					2nd dose					
Varicella (VAR)							◄---- 1st dose ----►					2nd dose					
Hepatitis A (HepA)					See Notes		2-dose series, See Notes										
Tetanus, diphtheria, acellular pertussis (Tdap ≥7 yrs)														Tdap			
Human papillomavirus (HPV)														See Notes			
Meningococcal (MenACWY-D ≥9 mos, MenACWY-CRM ≥2 mos)			See Notes											1st dose		2nd dose	
Meningococcal B														See Notes			
Pneumococcal polysaccharide (PPSV23)											See Notes						

Range of recommended ages for all children

Range of recommended ages for catch-up immunization

Range of recommended ages for certain high-risk groups

Recommended based on shared clinical decision-making or *can be used in this age group

No recommendation/ not applicable

Child Abuse and Neglect 7

Learning Objectives

- ❑ Define physical, sexual, and psychological abuse
- ❑ Describe the epidemiology of child abuse

INTRODUCTION

Table 7-1. Scope of Child Abuse and Neglect

Physical		Psychological	
Abuse	**Neglect**	**Abuse**	**Neglect**
Fractures Bruises Burns	Food Clothing Schooling Medical care Safety	Terrorizing Putting down Comparing Insulting	Love Support Stimulation Recognition

Definitions

- **Child maltreatment:** abusive actions or acts of commission and lack of action, or acts of omission that result in morbidity or death
- **Physical abuse:** intentional injury to a child by a caregiver that results in bruises, burns, fractures, lacerations, punctures, or organ damage; may be accompanied by short- or long-term emotional consequences
- **Psychological maltreatment:** intentional verbal/behavioral acts or omissions such as withholding emotional responsiveness, isolating, terrorizing that result in adverse emotional consequences
- **Sexual abuse:** any act intended for sexual gratification of an adult
- **Factitious disorder:** intentionally giving poisons or toxins, or any other deceptive action to simulate a disorder

The consequences of child abuse and neglect are severe. Failure-to-thrive (FTT) (nutritional neglect) is the most common cause of underweight infants (>50% of all cases of FTT). Additionally, developmental delay and learning disabilities are common. Physical disabilities may occur, and possibly death.

Note

In all 50 states, physicians and child care providers are required to report suspected abuse/neglect. Failure to report may result in penalties or malpractice claims for damages.

- Affords lawsuit protection to those who report in good faith
- Allows for all clinical and lab evaluation and documentation without parents' permission

Epidemiology

There is a higher likelihood of abuse with caregivers who have history of abuse or violence:

- Young parental age
- Closely spaced pregnancies
- Lower socioeconomic status
- On military bases
- Spousal abuse
- Substance abuse
- Single parent (mother)
- Intellectually disabled child
- High stress level
- Preterm, low-birth-weight infants

Note

Certainty is **not** required to file a report to Child Protective Services (CPS). However, one must determine whether parents have an understanding of disease processes and the intellectual, emotional, economic, and physical resources to provide for the child.

PHYSICAL ABUSE

A 2-year-old boy presents to the emergency department with a skull fracture that the mother states resulted after he fell from the sofa onto a carpeted floor. On physical examination the child is alert. He is noted to have old bruising on the buttocks and back, as well as a cigarette burn on his palm. The mother states that the child "falls a lot" and is always touching things he should not.

Diagnosis

- When to suspect
  - Injury is unexplained or implausible
  - Injury is incompatible with the history given or with child's level of development
  - There are no reports of death or serious brain injury from witnessed falls <10 feet.

Clinical Findings

Note

Battered child syndrome is suggested by bruises, scars, internal organ damage, and fractures in various stages of healing.

Bruises

- Most common
- Accidental: thin, leading surfaces overlying bone edges (e.g., shins)
- Nonaccidental: buttocks, genitals, back, back of hands, thoracoabdominal
- Shape of injury suggests object used: suspect with bilateral, symmetric, or geometric injuries
- Staging: **bruises in various stages are not compatible with a single event**
- Consider cultural issues, e.g., coining, cupping

Fractures

- Wrenching or pulling an extremity → corner **chip** or **bucket handle fracture** of metaphysis
- Inflicted fracture of bone shaft → more likely are **spiral fractures** from twisting rather than transverse from impact
- **A spiral fracture of the femur before child can walk independently has usually been inflicted by someone else.**
- Accidental impact rarely causes rib fracture or retinal hemorrhage in children
- Highly specific for abuse
  - Rib fractures in infants
  - Fractures of different stages of healing
  - Bilateral fractures
  - Complex skull fracture

Note

Differential Diagnosis

With osteogenesis imperfecta or severe osteomalacia, there is an increased incidence of pathologic fractures, **but** they are rarely of the metaphysis.

Burns

- Cigarette burns → circular, punched-out lesions of uniform size
- Immersion burns (most common in infants)
  - Glove-stocking pattern of extremity
  - Dipping into bathtub water:
    - Demarcation is uniform and distinct
    - Flexion creases spared; hands and feet spared
    - No splash burns
    - **Incompatible with falling into tub or turning on hot water while in tub**

Intentional head trauma

- Most common cause of death
- **Consider when injured infant presents with coma, convulsions, apnea, increased ICP**
- A subdural hemorrhage in which there are no scalp marks or skull fracture is possibly from a hand blow.
- Retinal hemorrhages
- Shaking—acceleration-deceleration; may have no external marks; 85% associated with retinal hemorrhage

Intra-abdominal injuries

- Impacts
- Recurrent vomiting, abdominal distension, absent bowel sounds, localized tenderness, shock
- If struck with fist → row of 3–4 teardrop-shaped, 1-cm bruises in a slight curve
- May rupture liver or spleen
- Laceration of small intestine at sites of ligamental support
- Intramural hematoma → temporary obstruction
- Free air

Note

Always obtain a CT scan for intracranial bleeding and an eye exam for retinal hemorrhages.

Laboratory studies

- **Skeletal survey when you suspect abuse in child age <2 years; in child >2 years, appropriate film area of injury, complete survey not usually required**
- If infant is severely injured **despite** absence of CNS findings
  - Head CT scan
  - ± MRI
  - Ophthalmologic examination
- If abdominal trauma
  - Urine and stool for blood
  - Liver and pancreatic enzymes
  - Abdominal CT scan
- For any bleeding, bruises: PT, PTT, platelets, bleeding time, INR

Management

The first step is always to institute **prompt medical, surgical, or psychological treatment.**

- Consider separating child from caregiver in exam area.
- Report any child **suspected** of being abused or neglected to CPS; caseworker confers with MD
- Law enforcement agency performs forensics, interviews suspects, and if criminal act has taken place, informs prosecutor (state by state)
- Initial action includes a phone report, then, in most states, a written report is required within 48 hours
- **Hospitalization is required if**
  - **Medical condition requires it**
  - **Diagnosis is unclear**
  - **There is no alternative safe place**
  - **Parents refuse hospitalization/treatment; MD must get emergency court order**
- MD should explain to parents
  - Why an inflicted injury is suspected
  - That MD is legally obligated to report
  - That referral is made to protect the child
  - That family will be provided with services
  - That a CPS worker and law enforcement officer will be involved
- Court ultimately decides guilt and disposition

Prognosis

The earlier the age of abuse, the greater the risk of mortality.

SEXUAL ABUSE

A 3-year-old girl presents with green vaginal discharge. Microscopic examination of the discharge reveals gram-negative intracellular diplococci.

- Epidemiology
  - Least common offender is a stranger
  - Most common reported abuse is that of daughters by fathers and stepfathers
  - **Most common overall is brother-sister incest**
  - Violence is not common but increases with age and size of victim
  - More likely to occur as a single incident with a stranger
- Clinical findings: sexual abuse should be **considered as a possible cause** if presenting with
  - Vaginal, penile, or rectal pain, discharge, bruising, erythema, or bleeding
  - Chronic dysuria, enuresis, constipation, or encopresis
  - **Any STIs in prepubertal child**
- Diagnosis
  - Test for pregnancy
  - Test for STIs
  - Test for syphilis, HIV, gonorrhea, hepatitis B
- Management:
  - If abuse suspected: report to CPS and police
  - If ≤72 hrs or any time with acute symptoms or acute psychiatric symptoms: send to acute sexual abuse referral center for immediate exam (videotaped forensic exam)
  - If >72 hrs or no acute symptoms: perform nonacute exam by healthcare professional with experience in evaluation of child with sexual abuse

Clinical Recall

Which of the following is most concerning for child abuse?

A. Bruising over the right shin

B. Buckle fracture of the distal radius

C. Candidal rash in groin

D. Metaphyseal fracture of the distal femur

E. Poorly demarcated burns on the hands

Answer: D

Note

Condyloma appearing after age 3 and *Trichomonas vaginalis* are probable diagnoses.

HSV-1 and nonvenereal warts may be autoinoculated.

Respiratory Disease 8

Learning Objectives

- ❑ Demonstrate understanding of upper airway obstruction from foreign bodies, congenital anomalies, and acute inflammatory upper airway obstruction
- ❑ Answer questions about inflammatory and infectious disorders of the small airways
- ❑ Describe the epidemiology and treatment of cystic fibrosis
- ❑ Recognize risk factors and presentation of sudden infant death syndrome

ACUTE INFLAMMATORY UPPER AIRWAY OBSTRUCTION

Croup

A 12-month-old child is brought to your office because of a barky cough. The mother states that over the past 3 days the child has developed a runny nose, fever, and cough. The symptoms are getting worse, and the child seems to have difficulty breathing. He sounds like a seal when he coughs.

- Infective agents—parainfluenza types 1, 2, 3
- Age 3 months–5 years; most common in winter; recurrences decrease with increasing growth of airway
- Inflammation of subglottis
- Signs and symptoms/examination—upper respiratory infection 1–3 days, then **barking cough, hoarseness, inspiratory stridor**; worse at night, gradual resolution over 1 week
- Complications—hypoxia only when obstruction is complete
- Diagnosis—**clinical, x-ray not needed (steeple sign if an x-ray is performed)**
- Treatment is supportive plus:
  - Mild: corticosteroid then observe; if improved, then home but if worsens, treat as moderate croup
  - Moderate: nebulized epinephrine + corticosteroid, then observe; if improved, then home but if worsens, repeat epinephrine and admit to hospital
  - Severe: nebulized epinephrine and corticosteroid then admit to hospital (possibly PICU)

Epiglottitis

A 2-year-old child presents to the emergency center with her parents because of high fever and difficulty swallowing. The parents state that the child had been in her usual state of health but awoke with fever of 40 C (104 F), a hoarse voice, and difficulty swallowing. On physical examination, the patient is sitting in a tripod position. She is drooling, has inspiratory stridor, nasal flaring, and retractions of the suprasternal notch and supraclavicular and intercostal spaces.

Note

Epiglottitis is a medical emergency that requires anesthesia for immediate intubation/emergent cricothyroidotomy.

- Infective agents
  - *Haemophilus influenzae* type B (HiB) no longer number one (vaccine success)
  - Now combination of *Streptococcus pyogenes, Streptococcus pneumoniae, Staphylococcus aureus, Mycoplasma*
  - Risk factor—adult or unimmunized child
- Inflammation of epiglottis and supraglottis
- Signs and symptoms/examination—dramatic acute onset
  - High fever, sore throat, dyspnea, and rapidly progressing obstruction
  - **Toxic-appearing**, difficulty swallowing, drooling, **sniffing-position**
  - **Stridor is a late finding (near-complete obstruction)**
- Complications—complete airway obstruction and death
- Diagnosis
  - **Clinical first** (do nothing to upset child), controlled visualization (laryngoscopy) of **cherry-red, swollen epiglottis**; **x-ray not needed (thumb sign if x-ray is performed)** followed by immediate intubation
- Treatment
  - **Establish patent airway** (intubate)
  - Antibiotics to cover staphylococci, HiB, and resistant strep (antistaphylococcal plus third-generation cephalosporin)

Table 8-1. Croup and Epiglottitis

Feature	Croup	Epiglottitis
Etiology	• Parainfluenza 1, 2, 3	• *S. aureus* • *S. pneumonia, S. pyogenes* • *H. influenza* type B
Age	• Preschool	• Toddler-young school age
Timing	• Cool months	• Year round
Diagnosis Key Words	• Barking cough • Inspiratory stridor • If the patient gets worse: Inspiratory stridor ↓ Expiratory stridor (biphasic stridor) ↓ Stridor at rest	• Acute onset • Extremely sore throat • Cannot swallow • High fever • Sniffing position • Drooling • Inspiratory stridor later
Best Initial Test	• Clinical Dx • CXR not needed-but shows steeple sign	• Laryngoscopy
Most Accurate Test	• PCR for virus • Not needed clinically	• C and S from tracheal aspirate
Best Initial Treatment	• None or nebulized epinephrine if severe	• Airway (intubation)
Definitive Treatment (If Needed)	• Parenteral steroid – Most common-single dose IM Dexamethasone → – Observation	• Airway (tracheostomy if needed) + broad-spectrum antibiotics • Then per sensitivities

Clinical Recall

A 5-year-old boy has had a low-grade fever, runny nose, non-productive cough, and mild stridor for 2 days. He sounds like a seal when he coughs. He is non-toxic appearing and has no increased work of breathing. What is the next step?

A. Chest x-ray to evaluate for the steeple sign

B. Discharge with close follow-up if symptoms worsen

C. Nebulized epinephrine

D. Laryngoscopy

E. Parenteral steroids

Answer: B

CONGENITAL ANOMALIES OF THE LARYNX

Table 8-2. Anomalies of the Larynx

Laryngomalacia	Subglottic Stenosis	Vocal Cord Paralysis
Most frequent cause of stridor in infants due to collapse of supraglottic structures in inspiration	Second most common cause	Third most common cause; may occur as a result of repair of congenital heart disease or TE-fistula repair(recurrent laryngeal nerve)
Clinical: stridor in supine that decreases in prone; exacerbated by exertion	Clinical: recurrent or persistent stridor with no change in positioning	Clinical: often associated with Chiari malformation (hydrocephalus); inspiratory stridor, airway obstruction, cough, choking, aspiration
Diagnosis: laryngoscopy	Diagnosis: laryngoscopy	Diagnosis: flexible bronchoscopy
Treatment: supportive; most improve in 6 months but surgery may be needed in severe cases	Treatment: cricoid split reconstruction	Treatment: supportive; most improve in 6-12 months but tracheostomy may be needed

AIRWAY FOREIGN BODY

A toddler presents to the emergency center after choking on some coins. The child's mother believes that the child swallowed a quarter. On physical examination, the patient is noted to be drooling and in moderate respiratory distress. There are decreased breath sounds on the right with intercostal retractions.

Note

Larynx is the most common site of foreign body aspiration in children age <1 year.

In children age >1 year, think trachea or right mainstem bronchus.

- Most seen in children age 3–4 years
- Most common foreign body is peanuts
- Highly suggested if symptoms are *acute* choking, coughing, wheezing; often a witnessed event
- Clinical—depends on location
  - Sudden onset of respiratory distress
  - Cough, hoarseness, shortness of breath
  - Wheezing ((asymmetric) and decreased breath sounds (asymmetric))
- Complications—obstruction, erosion, infection (fever, cough, pneumonia, hemoptysis, atelectasis)
- Diagnosis—Chest x-ray reveals air trapping (ball-valve mechanism). **Bronchoscopy** for definite diagnosis.
- Therapy—removal by **rigid bronchoscopy**

INFLAMMATORY DISORDERS OF THE SMALL AIRWAYS

Bronchiolitis

A 6-month-old infant presents to the physician with a 3-day history of upper respiratory tract infection, wheezy cough, and dyspnea. On physical examination, the patient has a temperature of 39 C (102 F), respirations of 60 breaths/min, nasal flaring, and accessory muscle usage. The patient appears to be air hungry, and the oxygen saturation is 92%.

- Infective agents—**respiratory syncytial virus** (**RSV**) (50%), parainfluenza, adenovirus, other viruses
- Typical age—almost all children infected by age <2 years, most severe at age 1–2 months in winter months.
- Inflammation of the small airways (inflammatory obstruction: edema, mucus, and cellular debris) → (bilateral) obstruction → air-trapping and overinflation
- Clinical presentation
  - Signs and symptoms:
    - Mild URI (often from household contact), decreased appetite and fever, irritability, paroxysmal wheezy cough, dyspnea, and tachypnea
    - **Apnea** may be more prominent early in young infants.
  - Examination:
    - Wheezing, increased work of breathing, fine crackles, prolonged expiratory phase
    - Lasts average of 12 days (worse in first 2–3 days)
- Complications—bacterial superinfection, respiratory insufficiency and failure (worse in infants with small airways and decreased lung function)
- Diagnosis and Treatment (per AAP Clinical Practice Guidelines, based on research and clinical evidence)
  - Diagnosis is clinical. Radiography (nonspecific, viral) and lab studies (microbiology) should not be routinely used.
  - Treatment is primarily supportive; hospitalize per severity assessment based on history and physical. Should **not administer** nebulized albuterol, nebulized epinephrine, nebulized hypertonic saline or systemic (or nebulized) corticosteroids as there is lack of evidence for any of these anecdotal therapies.
- Prevention—monoclonal antibody to RSV F protein (preferred: palivizumab) in **high-risk patients only** (otherwise healthy infants with a gestational age of 29 weeks, 0 days or greater and during the first year of life to infants with hemodynamically significant heart disease or chronic lung disease of prematurity defined as preterm infants <32 weeks 0 days' gestation who require >21% oxygen for at least the first 28 days of life)

PNEUMONIA

A 3-year-old child presents to the physician with a temperature of 40 C (104 F), tachypnea, and a wet cough. The patient's sibling has similar symptoms. The child attends daycare but has no history of travel or pet exposure. The child has a decreased appetite but is able to take fluids and has good urine output. Immunizations are up to date.

- Definition—inflammation of the lung parenchyma
- Epidemiology
  - **Viruses are predominant cause in infants and children age <5 years**
    - Major pathogen—**RSV**
    - Others—parainfluenza, influenza, adenovirus
    - More in fall and winter
  - **Nonviral causes** more common in **children >5 years**
    - Most—***M. pneumoniae* and *C. pneumoniae*** (genus has been changed to *Chlamydophila*; but remains *Chlamydia* for trachomatis)
    - *S. pneumoniae* most common with focal infiltrate in children of all ages
    - Others in normal children—*S. pyogenes* and *S. aureus* (no longer HiB)

Table 8-3. Clinical Findings in Viral Versus Bacterial Pneumonia

	Viral	Bacterial
Temperature	↑	↑↑↑
Upper respiratory infection	++	—
Toxicity	+	+++
Rales	Scattered	Localized
WBC	Normal to ↓	↑↑↑
Chest x-ray	Streaking, patchy	Lobar
Diagnosis	Nasopharyngeal washings, PCR	Blood culture, transtracheal aspirate (rarely done)

- Clinical findings
  - Viral:
    - Usually several days of URI symptoms; low-grade fever
    - Most consistent manifestation is tachypnea
    - If severe—cyanosis, respiratory fatigue
    - Examination—scattered crackles and wheezing
    - **Difficult to localize source in young children with hyper-resonant chests; difficult to clinically distinguish viral versus nonviral**

  - Bacterial pneumonia:
    - **Sudden shaking chills with high fever, acute onset**
    - Significant cough and chest pain
    - Tachypnea; productive cough
    - Splinting on affected side—minimize pleuritic pain
    - Examination—diminished breath sounds, localized crackles, rhonchi early; with increasing consolidation**, markedly diminished breath sounds and dullness to percussion**
  - *Chlamydia trachomatis* pneumonia:
    - No fever or wheezing (serves to distinguish from RSV)
    - **1–3 months of age**, with insidious onset
    - May or may not have conjunctivitis at birth
    - Mild interstitial chest x-ray findings
    - **Staccato cough**
    - **Peripheral eosinophilia**
  - *Chlamydophila pneumoniae* and *mycoplasma pneumoniae*
    - Cannot clinically distinguish
    - Atypical, insidious pneumonia; constitutional symptoms
    - **Bronchopneumonia**; gradual onset of constitutional symptoms with persistence of cough and hoarseness; coryza is unusual (usually viral)
    - Cough worsens with dyspnea over 2 weeks, then gradual improvement over next 2 weeks; becomes more productive; **rales** are most consistent finding (basilar)
- Diagnosis
  - Chest x-ray confirms diagnosis:
    - Viral—**hyperinflation with bilateral interstitial infiltrates and peribronchial cuffing**
    - Pneumococcal—**confluent lobar consolidation**
    - *Mycoplasma*—unilateral or bilateral lower-lobe interstitial pneumonia; **looks worse than presentation**
    - *Chlamydia*—interstitial pneumonia or lobar; as with *Mycoplasma*, chest x-ray often looks worse than presentation
  - White blood cells:
    - Viral—usually <20,000/mm^3 with lymphocyte predominance
    - Bacterial—usually 15,000–40,000/mm^3 with mostly granulocytes
    - *Chlamydia*—**eosinophilia**
  - Definitive diagnosis:
    - Viral—isolation of virus or detection of antigens in respiratory tract secretions; (usually requires 5–10 days); rapid reagents available for RSV, parainfluenza, influenza, and adenovirus
    - Bacterial—isolation of organism from blood (positive in only 10–30% of children with *S. pneumoniae*), pleural fluid, or lung; **sputum cultures are of no value in children.** For mycoplasma get PCR (had been IgM titers). PCR is also becoming the test of choice for viruses.

- Treatment
  - Based on presumptive cause and clinical appearance
  - Hospitalized—parenteral ampicillin (if *S. aureus* suspected, add vancomycin or clindamycin)
  - **If suspect viral (outpatient, mild)—may withhold treatment *if* mild and no respiratory distress. Up to 30% may have coexisting bacterial pathogens**; deterioration should signal possible secondary bacterial infection and should start empiric treatment.
  - ***Chlamydophila* or *Mycoplasma*—erythromycin** or other macrolide

Table 8-4. Pneumonia

Feature	Bacterial	Viral	*C. trachomatis*	*M. pneumoniae or C. pneumonia*
Etiology	• S. pneumoniae • HIB • S. aureus	• *RSV* • *Parainfluenza* • *Influenza* • *Adenovirus*	C. Trachomatis	• *M. Pneumoniae* • *C. Pneumonia*
Age	• Any age • Most common reason for lobar is *S. pneumoniae*	Most common form <5 years	Age 1–3 months	Most common form age >5 years
Timing	More in cold months	Cold months	All year	All year; more in winter
Diagnosis Key Words	• Acute • Severe • Productive cough • Dyspnea • High fever • Chest pain • Rhonchi • Rales • Decreased breath sounds • May have empyema	• Insidious • Often worsening URI • Lower temperature • Wheeze • Cough • Mild dyspnea	• May have had conjunctivitis as newborn • Afebrile • No wheeze • Staccato cough	• Insidious • URI symptoms with persistence of cough worsening over 2 weeks • Rales most consistent finding (lower lobe uni- or bilateral)
Best Initial Test	• CXR = lobar consolidation	• CXR = bronchopneumonia, interstitial • Hyperinflation with increased peribronchial markings	• CXR = mild interstitial	• CXR most unilateral lower lobe interstitial • Classically looks worse than symptoms
Most Accurate Test	• Sputum C and S (cannot rely on in child) • Blood culture • Pleural fluid culture	Respiratory secretions for viral or antigen isolation (would not do routinely)	Sputum PCR (but not needed = classic clinical diagnosis)	PCR of NP or throat swab (but not usually needed)
Best Initial Treatment and Definitive Treatment	• Admit for IV cefuroxime • Then change if needed based on C and S	• No treatment of viral pneumonia • If uncertain, give oral amoxicillin	Oral macrolide	Oral macrolide

Clinical Recall

A 15-month-old girl presents to the outpatient clinic on a winter afternoon with fever, shortness of breath, and wheezing. If a chest x-ray revealed hyperinflated lungs with peribronchial cuffing without consolidation, what would be the likely diagnosis?

A. Epiglottitis

B. Croup

C. Chlamydia pneumonia

D. Viral pneumonia

E. Pneumococcus

Answer: D

CYSTIC FIBROSIS (CF)

A 3-year-old white child presents with rectal prolapse. She is noted to be in the less than 5th percentile for weight and height. The parents also note that she has a foul-smelling bulky stool each day that "floats." They also state that the child has developed a repetitive cough over the last few months.

- Most common life-limiting recessive trait among whites
- Major cause of severe chronic lung disease and most common cause of exocrine pancreatic deficiency in children
- Primary pathogenic feature is dysfunction of epithelialized surfaces; obstruction and infection of airways; maldigestion
- Genetics
  - **Autosomal recessive**; CF gene most prevalent among **northern and central Europeans**
  - All of the gene mutations occur at a single locus on long arm of **chromosome 7.**
  - Codes for CF transmembrane regulator (**CFTR**—ion channel and regulatory functions)
    - Expressed mostly on epithelial cells of airways, gastrointestinal tract, sweat glands, genitourinary (GU) system
    - Not all children with CF can be identified by DNA testing; may need to sequence CFTR gene
- Pathogenesis and pathology
  - Membranes of CF epithelial cells **unable to secrete Cl^-** in response to cyclic adenosine monophosphate–mediated signals:
    - **Failure to clear mucous secretions**; paucity of water in mucous secretions
    - Increased salt content of sweat and other serous secretions

- Manifestations:
  - Bronchiolar obliteration, bronchiectasis (end-stage; severe destructive disease)
  - Opacified paranasal sinuses
  - Large nasal polyps
  - Pancreatic dysfunction; fat and fat-soluble vitamin malabsorption
  - Intestinal glands distended with mucous secretions; focal biliary cirrhosis
  - Endocervicitis
  - Body and tail of epididymis, vas deferens, seminal vesicles obliterated or atretic in males

- Clinical presentation
  - Intestinal tract—usually first presentation:
    - 10% of newborns with **meconium ileus**
      - X-ray shows dilated loops, no air–fluid levels, "ground-glass" (bubbly appearance) material in lower central abdomen
      - Gastrografin enema → reflux into ileum may clear; if not, then surgery
    - Most with malabsorption from pancreatic exocrine insufficiency → **frequent, bulky, greasy stools and failure-to-thrive.**
    - **Fat-soluble vitamin deficiency—ADEK**
    - Hepatobiliary—icterus, ascites, hepatomegaly, cholelithiasis, varices
    - Pancreas—increased incidence of diabetes mellitus, **acute pancreatitis**
    - **Rectal prolapse**—most in infants with steatorrhea, malnutrition, and cough
  - Respiratory tract:
    - **Rate of progression of lung disease is chief determinant of mortality and morbidity**—early in life—nontypeable *H. influenzae* and *S. aureus*, then colonization with *P. aeruginosa*, then later colonization with ***Burkholderia cepacia***: associated with rapid deterioration and death (end-stage)
    - **Cough, purulent mucus**—early in first year, extensive bronchiolitis, then pulmonary function test (PFT) abnormalities, dyspnea; finally, cor pulmonale, respiratory failure, and death; high risk for pneumothorax
    - Examination:
      - Increased A-P diameter
      - **Hyper-resonance**, rales, **expiratory wheezing**
      - **Clubbing**, cyanosis (late)
      - Sinuses almost always opacified
  - Genitourinary tract:
    - Delayed sexual development
    - Almost all males with **azoospermia**
    - Increased incidence of hernia, hydrocele, undescended testes
    - Females: **secondary amenorrhea**, cervicitis, **decreased fertility**
  - Sweat glands:
    - Excessive loss of salt → salt depletion, especially with hot weather or gastroenteritis (serum–hypochloremic alkalosis)
    - **Salty taste of skin**

- Diagnosis

Table 8-5. Diagnosing CF

Any of the Following	*Plus* Any of the Following
• Typical clinical features • History of a sibling with CF • Positive newborn screen	• Two increased sweat chlorides on 2 separate days • Identification of 2 CF mutations (homozygous) • Increased nasal potential difference

  - Sweat test (**best test**):
    - Difficult in first weeks of life
    - Confirm positive results
    - Diagnosis: >60 mEq/L
  - If sweat test is equivocal:
    - Increased potential difference across nasal epithelium
    - Pancreatic function—72-hour fecal fat collection, stool for trypsin, pancreozymin-secretin stimulation, serum immunoreactive trypsinogen (↑ in neonates)
  - X-rays:
    - Hyperinflation of chest
    - Nodular densities, patchy atelectasis, confluent infiltrates, hilar nodes
    - With progression—flattening of diaphragm, sternal bowing, narrow cardiac shadow; cysts, extensive bronchiectasis
  - Pulmonary function tests:
    - By 5 years—**obstructive** pulmonary disease
    - Then **restrictive (fibrosis)**
  - Microbiologic—finding in sputum of ***S. aureus*** first, followed by ***P. aeruginosa*** (mucoid forms) is **virtually diagnostic** (also *B. cepacia*, but is usually late finding)
  - Genetic:
    - Antenatal diagnosis by mutational analysis in family previously identified by birth of child with CF
    - Test spouse of carrier with standard panel of probes
    - **Newborn screen**—determination of immunoreactive trypsinogen in blood spots and then **confirmation with sweat or DNA testing; does *not* improve pulmonary and therefore long-term outcome**
- Treatment
  - Clear airway secretions and control infections:
    - **Aerosol treatment; albuterol/saline**
    - Daily dose of **human recombinant DNase (mucolytic)**
    - Chest physical therapy with postural drainage: 1–4 times per day
  - Antibiotics:
    - For acute infections (change in baseline condition)
    - Most frequent is *P. aeruginosa* (also non-typable *H. influenzae*, *S. aureus*, *B. cepacia*)
    - Must base choice on culture and sensitivity
    - Aerosolized antibiotics—**tobramycin**

  - Hospitalization:
    - Progressive despite intensive home measures
    - Typical 14-day treatment
    - Two-drug regimens to cover *Pseudomonas*, e.g., **piperacillin plus tobramycin or ceftazidime**
  - Nutritional: **pancreatic enzyme replacement with meals/snacks; vitamin supplementation (ADEK)**
  - **Adequate fluid replacement when exercising or hot weather**
  - Ivacaftor for certain mutations
  - Lung transplant

SUDDEN INFANT DEATH SYNDROME (SIDS)

A 2-month-old term infant born with no complications via spontaneous vaginal delivery is brought to the emergency center via ambulance with CPR in progress. According to the mother, the patient was in his usual state of good health until 4 A.M. when she found him cyanotic and not breathing. At midnight the infant was fed 4 ounces of formula without any difficulty and then placed to sleep in a crib. At 4 A.M. the mother returned and found the child unresponsive. She immediately called emergency medical services and began CPR. The child was pronounced dead on arrival to the emergency department.

- Sudden death of an infant, unexplained by history or by thorough postmortem examination including autopsy, investigation of death scene, and review of medical history; recently, new nomenclature is **Sudden Unexplained Infant Death Syndrome** (SUIDS)
- Before 1992, incidence was constant at 1.4 in 1,000; then with **Back to Sleep** campaign, down to 0.45 in 1,000
- Differential diagnosis
  - Explained at autopsy: infections; congenital anomaly; unintentional injury; traumatic child abuse; other natural causes
  - Not explained: SIDS; **intentional suffocation**
- Pathology: no findings are pathognomonic and none are diagnostic (markers for preexisting, chronic, low-grade asphyxia): **petechial hemorrhages**; pulmonary edema
- Environmental risk factors
  - Nonmodifiable:
    - Low socioeconomic status
    - African American and Native American
    - **Highest at 2–4 months** of age; most by 6 months
    - Highest in winter, midnight to 9 A.M.
    - Males > females

Note

Sudden unexpected infant death (SUID) is the death of an infant age <1 year that occurs suddenly, and whose cause of death is not immediately obvious. Most SUIDs are one of 3 types.

- SIDS
- Unknown cause
- Accidental suffocation and strangulation in bed

  - Modifiable:
    - Shorter interpregnancy interval
    - Less prenatal care
    - Low birth weight, preterm, intrauterine growth retardation
    - **Maternal smoking**
    - **Postnatal smoking**
- **Sleep environment**
  - **Higher incidence related to prone sleeping**
  - **Supine position now better than side-lying**
  - No increased problems in supine, i.e., aspiration
  - Higher incidence with **soft bedding/surfaces**
  - Higher incidence with **overheating**
  - Pacifier shown to consistently decrease risk
- Other risk factors
  - Episode of an apparent life-threatening event (ALTE); recently, new nomenclature for ALTE is **Brief Resolved Unexplained Episode** (BRUE)
  - Subsequent sibling of SIDS victim
  - Prematurity—inverse with gestational age and birth weight
- **Home monitors do not decrease risk.**
- Reducing risk
  - **Supine while asleep**
  - Use crib that meets federal safety standards
  - No soft surfaces (sofas, waterbeds, etc.)
  - No soft materials in sleep environment
  - No bed-sharing
  - Avoid overheating and overbundling
  - Use prone position only while infant is awake and observed
  - No recommendation for home monitoring for this purpose
  - Expand national Back to Sleep campaign (up to 25% of infants still sleep prone).

Clinical Recall

You are offering advice to a new mother as she and her newborn are about to be discharged home after an uneventful delivery. The mother asks about sudden infant death syndrome (SIDS) and wants to learn more. What is an appropriate response?

A. Pacifiers should be avoided

B. Prone sleeping is a preventative strategy

C. The underlying cause is determined by autopsy

D. Bilateral retinal hemorrhages are pathognomonic

E. There is a higher risk in infants of women who smoke

Answer: E

Allergy and Asthma 9

Learning Objective

❑ Apply knowledge of allergies and asthma to diagnose and describe treatment options

ALLERGIES

Allergic Rhinitis

Allergic rhinitis is generally established by age 6. Risk factors include early introduction of formula (versus breast milk) or solids, mother smoking before child is age 1 year, and heavy exposure to indoor allergens.

- Most perennial or mixed; increased symptoms with greater exposure
- **Diagnosis suggested by typical symptoms in absence of URI or structural abnormality (nasal congestion/pruritus, worse at night with snoring, mouth-breathing; watery, itchy eyes; postnasal drip with cough; possible wheezing; headache)**
- Specific behaviors
  - Allergic salute (rhinorrhea and nasal pruritus) → nasal crease
  - Vigorous grinding of eyes with thumb and side of fist
- History of symptoms
  - Timing and duration (seasonal versus perennial)
  - Exposures/settings in which symptoms occur
  - Family history of allergic disease (atopy, asthma)
  - Food allergies more common (nuts, seafood) in young children (then skin, gastrointestinal, and, less often, respiratory)
- Physical examination
  - **Allergic shiners** (venous stasis)—blue-gray-purple beneath lower eyelids; often with **Dennie lines**—prominent symmetric skin folds
  - Conjunctival injection, **chemosis** (edema), stringy discharge, "cobblestoning" of tarsal conjunctiva
  - **Transverse nasal crease (from allergic salute)**
  - **Pale nasal mucosa**, thin and clear secretions, **turbinate hypertrophy**, polyps
  - Postnasal drip (posterior pharynx)
  - Otitis media with effusion is common

- Differential diagnosis
  - **Nonallergic inflammatory rhinitis (no IgE antibodies)**
  - **Vasomotor rhinitis (from physical stimuli)**
  - **Nasal polyps (think of CF)**
  - **Septal deviation**
  - **Overuse of topical vasoconstrictors**
  - Rare: neoplasms; vasculitides; granulomatous disorders (Wegener)
- Laboratory evaluation (no initial routine labs; clinical DX)
  - In vitro:
    - Peripheral eosinophilia
    - Eosinophils in nasal and bronchial secretions; **more sensitive than blood eosinophils**
    - Increased serum IgE
    - Allergen-specific IgE in blood draw (**advantages** are safety and the results will be uninfluenced by skin disease/medications, while major **disadvantages** are its expense and less sensitivity); best use is for extensive dermatitis and for medications that interfere with mast cell degranulation, have high risk for anaphylaxis, or cannot cooperate with skin tests
  - In vivo—**skin test (best):**
    - Use appropriate allergens for geographic area plus indoor allergens.
    - May not be positive before 2 seasons
- Treatment—environmental control plus removal of allergen is **most effective method**
  - Avoidance of biggest triggers—house dust mite, cat, cockroach
  - Dehumidifiers, HEPA-filtered vacuuming, carpet removal, pillow and mattress encasement
  - Remove pets
  - No smoking
  - No wood-burning stoves/fireplaces
- Pharmacologic control
  - **Antihistamines (first-line therapy)**:
    - First generation—diphenhydramine, chlorpheniramine, brompheniramine; cross blood-brain barrier—sedating
    - **Second generation (cetirizine, fexofenadine, loratadine)**—nonsedating (**now preferred drugs**); easier dosing
    - **Oral antihistamines are more effective than cromolyn but significantly less than intranasal steroids; efficacy ↑ when combined with an intranasal steroid**
  - Intranasal corticosteroids—**most effective medication, but not first-line**:
    - Effective for all symptoms
    - Add to antihistamine if symptoms are more severe
  - Leukotriene-receptor antagonists
  - Chromones—cromolyn and nedocromil sodium:
    - Least effective
    - Very safe with prolonged use
    - Best for preventing an unavoidable allergen

Note

Differential Diagnosis of Eosinophilia

- Neoplasms
- Asthma/Allergy
- Addison disease
- Collagen Vascular Disorders
- Parasites

  - Decongestants—(alpha-adrenergic → vasoconstriction)—topical forms (oxymetazoline, phenylephrine) significant **rebound** when discontinued.
  - Epinephrine—alpha and beta adrenergic effects; **drug of choice for anaphylaxis**
  - Immunotherapy:
    - Administer gradual increase in dose of allergen mixture → decreases or eliminates person's adverse response on subsequent natural exposure
    - **Major indication**—duration and severity of symptoms are disabling in spite of routine treatment (for at least 2 consecutive seasons). This, however, is the **treatment of choice for insect venom allergy**.
    - **Should not** be used for (lack of proof): atopic dermatitis, **food allergy,** latex allergy, urticaria, children age <3 years (too many systemic symptoms)
    - Need several years of treatment; expensive
- Complications of allergic rhinitis
  - Chronic sinusitis
  - Asthma
  - Eustachian tube obstruction → middle ear effusion
  - Tonsil/adenoid hypertrophy
  - Emotional/psychological problems

Insect Venom Allergy

- Etiology/pathophysiology—systemic allergic responses are IgE-mediated and are almost always due to stings from the order Hymenoptera (yellow jackets most notorious—aggressive, ground-dwelling, linger near food)
- Clinical presentation
  - Local—limited swelling/pain <1 day
  - Large local area—develop over hours to days; extensive swelling
  - Systemic—urticaria/angioedema, pruritus, **anaphylaxis**
  - Toxic—fever, malaise, emesis, nausea
  - Delayed/late response—serum sickness, nephrotic syndrome, vasculitis, neuritis, encephalitis
- Diagnosis—for biting/stinging insects, **must pursue skin testing**
- Treatment
  - Local—cold compresses, topical antipruritic, oral analgesic, systemic antihistamine; **remove stingers by scraping**
  - **If anaphylaxis—epinephrine pen**, ID bracelet, avoid attractants (e.g., perfumes)
  - **Indication for venom immune therapy—severe reaction with + skin tests (highly effective in decreasing risk)**

Food Reactions

- Clinical presentation
  - Most infants and young children **outgrow milk and egg allergy** (half in first 3 years); majority with nut or seafood allergies retain for life:
    - **Most food allergies are to egg, milk, peanuts, nuts, fish, soy, wheat, but any food may cause a food allergy.**
    - **Food allergic reactions are most common cause of anaphylaxis seen in emergency rooms**

  - With food allergies, there is an **IgE and/or a cell-mediated response.**
  - Manifestations:
    - Skin—**urticaria/angioedema** and flushing, **atopic dermatitis;** 1/3 of children with atopic dermatitis have food allergies, but most common is acute urticaria/angioedema
    - Gastrointestinal—oral pruritus, nausea, **vomiting, diarrhea, abdominal pain,** eosinophilic gastroenteritis (**often first symptoms to affect infants**): predominantly a **cell-mediated response, so standard allergy tests are of little value; food protein–induced enterocolitis/proctocolitis presents with bloody stool/diarrhea** (**most cow milk or soy protein allergies**)
    - Respiratory—nasal congestion, rhinorrhea, sneezing, laryngeal edema, dyspnea, **wheezing, asthma**
    - Cardiovascular—dysrhythmias, **hypotension**
- Diagnosis
  - Must establish the food and amount eaten, timing, and nature of reaction
  - Skin tests, allergen-specific IgE is useful for IgE sensitization: a negative skin test excludes an IgE-mediated form but because of cell-mediated responses, patient may need a **food elimination and challenge test** in a controlled environment (**best test**)
- Treatment
  - **Only validated treatment is elimination**
  - **Epinephrine pens** for possible anaphylaxis

Clinical Recall

A 14-year-old-boy has persistent rhinorrhea, itchy eyes and nose, and post-nasal drip. He has no pets, does not smoke, and uses an allergen-free pillowcase. What is the first-line pharmacologic treatment?

A. Continue conservative management

B. Prescribe oral antihistamine

C. Prescribe intranasal corticosteroid

D. Prescribe intramuscular epinephrine

E. Prescribe inhaled steroids

Answer: B

Urticaria and Angioedema

Causes:

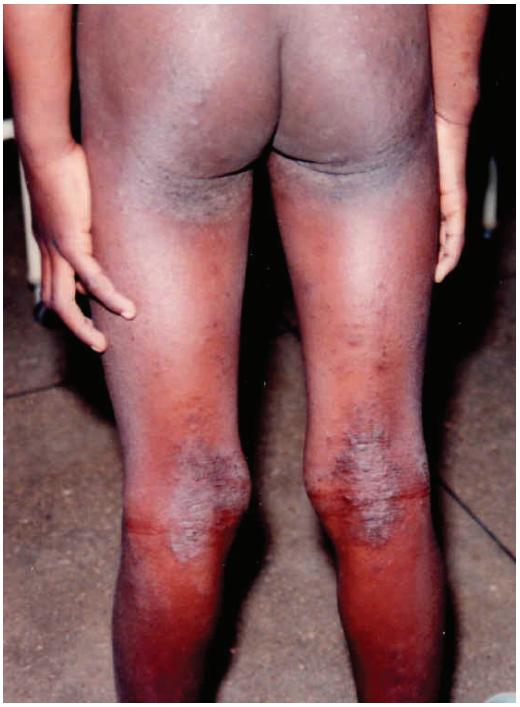
- Acute, IgE-mediated (duration ≤6 weeks)
  - Activation of mast cells in skin
  - Systemically absorbed allergen: food, drugs, stinging venoms; with allergy, penetrates skin → hives (urticaria)
- Non IgE-mediated, but stimulation of mast cells
  - **Radiocontrast agents**
  - Viral agents (especially EBV, hepatitis B)
  - Opiates, NSAIDs
- Physical urticarias; environmental factors—temperature, pressure, stroking, vibration, light
- Hereditary angioedema
  - Autosomal dominant
  - C1 esterase-inhibitor deficiency
  - Recurrent episodes of nonpitting edema
- Diagnosis mainly clinical; skin tests, IgE-specific allergens (blood)
- Treatment
  - Most respond to avoidance of trigger and oral antihistamine
  - Severe—epinephrine, short-burst corticosteroids
  - If H_1 antagonist alone does not work, **H_1** plus **H_2** antagonists are effective; consider steroids
  - For chronic refractory angioedema/urticaria → IVIg or plasmapheresis

Anaphylaxis

- Sudden release of active mediators with cutaneous, respiratory, cardiovascular, gastrointestinal symptoms
- Most common reasons
  - In hospital—**latex, antibiotics**, IVIg (intravenous immunoglobulin), radiocontrast agents
  - Out of hospital—food (**most common is peanuts**), insect sting, oral medications, idiopathic
- Presentation—reactions from ingested allergens are delayed (minutes to 2 hours); with injected allergen, reaction is immediate (more gastrointestinal symptoms)
- Treatment
  - What the patient should do immediately:
    - **Injectable epinephrine**
    - Oral liquid diphenhydramine
    - Transport to ER
  - Medical:
    - **Oxygen and airway management**
    - Epinephrine IM (IV for severe hypotension); intravenous fluid expansion; H_1 antagonist; corticosteroids; nebulized, short-acting beta-2 agonist (with respiratory symptoms); H_2 antagonist (if oral allergen)

Atopic Dermatitis (Eczema)

- Epidemiology/pathophysiology
  - Interaction among genetic, environmental, and immunologic factors; familial with strong maternal influence
  - Majority develop allergic rhinitis and/or asthma
  - Most have increased eosinophils and IgE
- Clinical presentation
  - **Half start by age 1 year**; most by age 1 and 5 years; chronic or relapsing
  - Intense cutaneous reactivity and **pruritus**; worse at night; scratching induces lesions; becomes excoriated
  - Exacerbations with foods, inhalants, bacterial infection, decreased humidity, excessive sweating, irritants
  - Patterns for skin reactions:
    - Acute: **erythematous papules, intensely pruritic, serous exudate and excoriation**
    - Subacute—erythematous, excoriated, **scaling papules**
    - Chronic—**lichenification** (thickening, darkening)



Courtesy of Tom D. Thacher, M.D.

Figure 9-1. Subacute and Chronic Atopic Dermatitis Most Commonly Affects the Flexural Surfaces of Joints

  - Distribution pattern:
    - Infancy: **face, scalp, extensor** surfaces of extremities
    - Older, long-standing disease: **flexural** aspects
    - Often have remission with age, but skin left prone to itching and inflammation when exposed to irritants

- Treatment
  - Identify and eliminate causative factors
  - **Cutaneous hydration**
    - **Dry skin, especially in winter (xerosis)**
    - Lukewarm soaking baths followed by application of occlusive emollient (hydrophilic ointments)
  - **Topical corticosteroids**
    - **Seven classes—the higher potency classes are not to be used on face or intertriginous areas and only for short periods**
    - **Goal—emollients and low-potency steroids for maintenance**
  - Topical immunomodulators; **tacrolimus** (calcineurin inhibitor):
    - Inhibits activation of key cells
    - Ointment safe and effective
    - **Safe on face**
    - Can use as young as age **2 years**
  - Tar preparations
  - Phototherapy—UV light
  - Systemic: antihistamines (sedating at night; for pruritus); glucocorticoids; cyclosporine (refractory to all other treatment); interferon (if all else fails)
  - Treat with antibiotics for bacterial superinfection
- Complications
  - Secondary bacterial infection, especially *S. aureus*; increased incidence of *T. rubrum, M. furfur*
  - Recurrent viral skin infections—**Kaposi varicelliform eruption (eczema herpeticum) most common**
  - Warts/molluscum contagiosum

ASTHMA

A 6-year-old boy presents to his physician with end-expiratory wheezing scattered throughout the lung fields. He is noted to have nasal flaring, tachypnea, and intercostal retractions. These symptoms are triggered by changes in the weather. He has a family history of asthma and atopic dermatitis. He has never been intubated or admitted to the pediatric ICU. His last hospitalization for asthma was 6 months ago. He takes medication for asthma only when he starts to wheeze.

- Etiology/pathophysiology
  - Chronic inflammation of airways with episodic at least partially reversible airflow obstruction
    - Genetic and environmental factors: concomitant allergies (perennial in most), induced by common viral agents, tobacco smoke; cold, dry air; strong odors
    - Most with onset age <6 years; most resolve by late childhood
    - Two main patterns:
      - Early childhood triggered primarily by common **viral infections**
      - Chronic asthma associated with **allergies** (often into adulthood; atopic)

  - **Some risk factors for persistent asthma:** perennial allergies; atopic dermatitis, allergic rhinitis, food allergy; severe lower respiratory tract infections; wheezing other than with URIs (exercise, emotions); environmental tobacco smoke exposure; low birth weight
- Clinical presentation
  - **Diffuse wheezing, expiratory then inspiratory**
  - **Prolonged expiratory phase**
  - Decreased breath sounds
  - Rales/rhonchi → excess mucus and inflammatory exudate
  - Increased work of breathing
  - Exercise intolerance

Table 9-1. Bronchiolitis Versus Asthma

Feature	Bronchiolitis	Asthma
Etiology	Most RSV	Reversible bronchoconstriction with chronic inflammation
Age	Infants (especially <1 year)	Most start age <5 years
Timing	• Winter	• All year • Most with URI in winter
Diagnosis Key Words	• URI from another household contact • Getting worse • Fever • Tachypnea • Bilateral expiratory wheezing ± respiratory distress • Apnea	• Repeated episodes of expiratory wheezing • Chronic non-productive cough • Chest tightness • Respiratory distress • May have other atopic disease + family history • May occur primarily with URIs • Cannot make diagnosis of asthma for first-time wheezing in infant with fever (diagnosis is bronchiolitis)
Best Initial Test	• Clinical Dx • CXR only if severe and therefore possibility of secondary bacterial pneumonia	Worsening of FEV1/FVC with exercise and improvement with beta-agonist
Most Accurate Test	• NP rapid test or PCR for organism • ABG only for severe to evaluate possible need for ventilation	• Repeated episodes that improve with beta-agonist
Treatment	• Oxygen, if needed • Supportive Rx • May try nebulized hypertonic saline • Ribavirin in severe or worsening cases MAY prevent the need for intubation and ventilation	• Oxygen • Short-acting beta-agonist • Add oral steroid for acute attack • May need chronic maintenance Rx

- Diagnosis
  - **In children, neither lab tests nor provocation challenge tests are required for diagnosis; they may support the clinical diagnosis or may be used to follow the patient clinically.**
  - Lung function:
    - **Gold standard = spirometry during forced expiration.** $FEV_1/FVC < 0.8$ = airflow obstruction (the forced expiratory volume in 1 second adjusted to the full expiratory lung volume, i.e., the forced vital capacity) in children age ≥ 5 yrs
    - Bronchodilator response to inhaled beta-agonist—improvement in FEV_1 to >12%
    - Exercise challenge—worsening in FEV_1 of at least 15%
    - **Home tool—peak expiratory home monitoring (PEF);** A.M. and P.M. PEF for several weeks for practice and to establish personal best and to correlate to symptoms; based on personal best, divide PEFs into zones: green (80–100%), yellow (50–80%), red (<50%)
  - Radiology (no routine use):
    - **Hyperinflation—flattening of the diaphragms**
    - **Peribronchial thickening**
    - Use to identify other problems that may mimic asthma (e.g., aspiration with severe gastroesophageal reflux) and for complications during severe exacerbations (atelectasis, pneumonia, air leak)
- Treatment—based on asthma severity classification
  - Intermittent: symptoms ≤2 days/week and ≤2 nights/mo
    - No need for daily controller
  - Persistent (mild → moderate → severe) symptoms > intermittent
    - Need daily controller

Table 9-2. Asthma Severity Classification and Treatment (simplified from National Asthma Education and Prevention Program)

Class	Daytime Symptoms	Nighttime Symptoms	Treatment
Intermittent	≤2×/week	≤2×/month	SABA for relief of acute symptoms
Mild persistent	>2×/week	>2×/month	Low-dose ICS
Moderate persistent	Daily	>1×/week	Increased dose ICS **or** (preferred) low-dose ICS + either LABA or LTRA SABA for relief of acute symptoms
Severe persistent	Continual; limited activities; frequent exacerbations	Frequent	Moderate- to high-dose ICS + either LABA or LTRA SABA for relief of acute symptoms

Note

With all asthma categories, a step-up, step-down dosing is typically used (high at first, then down to minimum necessary to prevent symptoms).

Note

Older children can use a metered dose inhaler (MDI); younger children often need to do so with a spacer and face mask. Infants may need to have nebulized medications.

Note

Adjunct Treatment to Prevent Intubation and Ventilation

- IV beta agonist
- IV theophylline
- Heliox (70:30 He:O_2); decreased airway resistance and clinical response in 20 min
- IV $MgSO_4$– smooth-muscle relaxant; monitor BP every 10–15 min (risk of hypotension)

- Asthma medications
  - **Quick-relief medications**
    - Short-acting beta-2 agonists: **albuterol, levalbuterol** (nebulized only), terbutaline, metaproterenol (rapid onset, may last 4–6 hrs; **drug of choice for rescue and preventing exercise-induced asthma but inadequate control if need >1 canister/month**
    - Anticholinergics (much less potent than beta agonists): **ipratropium bromide**; mostly for added treatment of acute severe asthma in ED and hospital
    - Short-course systemic glucocorticoids: outpatient for moderate to severe flare-up, and prednisone 3–7 days; inpatient recommended with IV methylprednisolone IV
- Management of asthma exacerbations
  - Emergency department:
    - Monitor, **oxygen** as needed
    - Inhaled **albuterol** q 20 minutes for 1 hour—add **ipratropium** if no good response for second dose
    - **Corticosteroids PO or IV**
    - Can go home if sustained improvement with normal physical findings and **SaO_2 >92% after 4 hours in room air**; PEF ≥70% of personal best
    - Home on q 3–4 hour **MDI + 3–7-day oral steroid**
  - Hospital—**for moderate–severe flare-ups without improvement within 1–2 hours of initial acute treatment with PEF <70% of personal best or SaO_2 <92% on room air**:
    - **Oxygen**
    - Nebulized **albuterol** (very frequently or continuous)
    - Add **ipratropium** q 6 hours
    - **Intravenous corticosteroids**
    - May need intravenous fluids
    - Mechanical ventilation (rare)

Clinical Recall

A 12-year-old girl is diagnosed with asthma. She has nighttime symptoms twice a week and daily daytime symptoms. Which of the following should NOT be part of her long-term treatment?

A. Inhaled steroids

B. Leukotriene-receptor antagonist

C. Short-acting beta agonist

D. Oral prednisone

E. Long-acting beta agonist

Answer: D

Immune-Mediated Disease 10

Learning Objectives

- ❑ Explain information related to evaluation of suspected immune deficiency
- ❑ Categorize specific defects of immune deficiency

EVALUATION OF SUSPECTED IMMUNE DEFICIENCY

Table 10-1. Suspecting Immunodeficiency by Major Defect

	B-Cell	T-Cell	Complement	Neutrophil
Common organism	**Recurrent bacterial:** streptococci, staphylococci, *Haemophilus, Campylobacter*; ***Viral:*** *enteroviruses;* *Uncommon: giardia, cryptosporidia*	**Opportunistic organisms:** CMV, EBV, varicella, *Candida*, Pneumocystis jiroveci, mycobacteria	*Pneumococci, Neisseria*	**Bacteria:** Staphylococci, *Pseudomonas, Serratia, Klebsiella, Salmonella;* **Fungi:** *Candida, Aspergillus*
Age onset	Age 5-7 months or later childhood to adult	Usually age 2-6 months	Any age	Early onset
Infections	Most are **recurrent sinopulmonary infections and recurrent enteroviral meningitis**	**Mucocutaneous candidiasis;** pulmonary and GI infections	**Meningitis,** arthritis, septicemia, recurrent sinopulmonary infections	**Skin abscesses**, impetigo, cellulitis, **suppurative adenitis**, gingivitis, **oral ulcers**, osteomyelitis, internal organ abscesses
Other findings	**Autoimmunity, lymphoreticular malignancy**	**Chronic diarrhea and failure-to-thrive**; postvaccination dissemination - varicella, BCG; hypocalcemia in infancy; **graft-versus-host** from transplacental maternal engraftment or nonirradiated blood	Autoimmune disorders, vasculitis, glomerulonephritis, **angioedema**	**Prolonged attachment of umbilical cord**, poor wound healing, decreased signs of infection
Best initial test	Screen with IgA→if low, measure IgG and IgM (**quantitative immunoglobulins**)	Lymphocyte count (low)	Screen is total hemolytic complement (CH_{50})—will be depressed if any component is consumed	Neutrophil count
Other tests	Low antibody titers to specific antigens—isohemagglutinins, vaccines	**Best cost-effective test for T-cell function – *Candida* skin test**	Identify mode of inheritance—all are autosomal except for properdin deficiency (X-linked)	Neutrophil respiratory burst after phorbol ester stimulation; most reliable now uses **rhodamine fluorescence (replaced the NBT test)**
Specific tests	Enumerate B-cells with **flow cytometry** (monoclonal antibodies to B-cell-specific CD antigens): B cell absent or present and number	Flow cytometry using monoclonal antibodies recognizing T-cell CD antigens (phytohemagglutinin, concanavalin A, pokeweed mitogen)	Can easily measure C3 and C4 (hereditary angioedema); others require a research lab	Can identify leukocyte adhesion deficiencies with flow cytometric assays of lymphocytes and neutrophils (CD18, CD11, CD15)

Note: For each, the **most accurate test** is **molecular genetic diagnosis**.

SPECIFIC DEFECTS

Defects of Antibody Production

X-linked (Bruton) agammaglobulinemia

X-linked (Bruton) agammaglobulinemia (XLA) is a profound **defect in B-cell development** which leads to an absence of circulating B cells and thus leads to severe hypogammaglobulinemia **with small-to-absent tonsils and no palpable lymph nodes.**

- **Genetics:** >500 known mutations of the Btk gene (Bruton tyrosine kinase), which is necessary for pre-B-cell expansion and maturation; long arm of **X-chromosome**
- **Clinical findings: boys with pyogenic sinopulmonary infections**
- **Diagnosis:** clinical presentation + **lymphoid hypoplasia on exam; all immunoglobulins severely depressed**; flow cytometry shows absence of circulating B-cells; gene sequencing for specific mutation
- **Treatment:** appropriate use of antibiotics + **regular monthly IVIG**

NOTE: The only 2 B-cell defects for which stem cell transplantation is recommended are CD40 ligand defect (extremely rare; one of the known mutations on the X-chromosome for hyper-IGM syndrome) and X-linked lymphoproliferative disease.

Common variable immunodeficiency

Common Variable Immunodeficiency (CVID) is hypogammaglobulinemia with phenotypically normal B-cells; **blood B-lymphocytes do not differentiate into IG-producing cells**

- **Genetics:** majority have no identified molecular diagnosis, so are sporadic; may have a common genetic basis with selective IgA deficiency (occurs in families together and some later with IgA may develop CVID)
- **Clinical findings:** boy or girl (**equal sex distribution**) with **later onset infections**, less severe; clinically similar to XLA, but rare echovirus meningoencephalitis
- **Diagnosis:** clinical presentation + serum IG and antibody deficiencies as profound or less than in XLA; **normal sized lymphoid tissue; later autoimmune disease and malignancy (lymphoma)**
- **Treatment:** need to be **screened for anti-IgA antibodies** (as in selective IgA deficiency)→ if present, therapy consists of the one IG preparation available that contains no IgA.

Selective IgA deficiency

Selective IgA deficiency is the **most common immunodeficiency**. It is caused by the absence or near absence of serum and secretory IgA with phenotypically normal B-cells

- **Genetics:** basic defect is unknown; boys and girls and **familial pattern** suggests autosomal dominant with variable expression; **also seen in families with CVID** (as above); both may be triggered by environmental factors
- **Clinical findings:** same bacteria as others with most infections in **respiratory, GI and urogenital** tracts; giardiasis is common

- **Diagnosis: very low-to-absent serum IgA with other IGs normal**; as with CVID, incidence of autoantibodies, autoimmune disease and malignancy increased; **serum antibodies to IgA can cause severe anaphylactic reactions if any blood product with IgA is administered (NOT a transfusion reaction)**
- **Treatment: IVIG is not indicated** (95–99% is IgG) because if usual IVIG (containing IgA) product is given, patients are at risk for severe reaction. Additionally, because it is specifically an IgA deficiency, the IVIG product with the IgA removed cannot be used. Treat the infections (generally milder).

Defects of Cellular Immunity (T-cell Defects)

DiGeorge syndrome (thymic hypoplasia)

DiGeorge syndrome is thymic and parathyroid hypoplasia to aplasia from **dysmorphogenesis of the 3rd and 4th pharyngeal pouches**. Other structures are also involved: great vessel anomalies (right-sided aortic arch, interrupted aortic arch), esophageal atresia, bifid uvula, congenital heart disease (conotruncal malformations, septal defects), facial dysmorphism (short philtrum, thin upper lip, hypertelorism, mandibular hypoplasia, low-set, often notched ears), and cleft palate.

- **Genetics: microdeletions of 22q11.2** (DiGeorge syndrome chromosomal region, DGCR); 22q deletions also seen in velocardiofacial syndrome and conotruncal anomaly face syndrome (**CATCH 22 syndromes:** Cardiac, Abnormal facies, Thymic hypoplasia, Cleft palate, Hypocalcemia); partial DiGeorge is more common, with variable thymic and parathyroid hypoplasia. About 1/3 with complete DiGeorge have the **CHARGE association**. Must confirm diagnosis for complete form by molecular genetics (fatal without definitive treatment).
- **Clinical findings:** from almost no infections with normal growth to **severe opportunistic infections and graft-versus-host disease. In most, initial presentation is neonatal hypocalcemic seizures.**
- **Diagnosis:** most with only moderately low absolute lymphocyte counts with variably decreased CD3 T-lymphocytes per the degree of thymic hypoplasia and variable response to mitogen stimulation. **Must get a T-cell count on all infants born with primary hypoparathyroidism, CHARGE, truncus arteriosus and interrupted aortic arch**
- **Treatment:** complete form correctable with either culture unrelated thymic tissue transplants or bone marrow or peripheral blood transplantation from HLA-identical sibling

Note

The rest of the isolated T-cell defects are extremely rare, known only to immunologists. They are not seen on the exam.

Combined Antibody and Cellular Immunodeficiencies

Severe combined immunodeficiency

Severe Combined Immunodeficiency (SCID) is the absence of all **adaptive immune function**, and in some, **natural killer cells** due to diverse mutations. It is the most severe immunodeficiency known.

- **Genetics:** mutations of any one of 13 genes encoding the components of immune system critical for lymphoid cell development; result in very small thymuses which

fail to descend from the neck and a lack of normal components + splenic depletion of lymphocytes and absent (or very undeveloped) remaining lymphatic tissue. X-linked SCID is the most common form in the United States.

- **Clinical findings: first 1-3 months of life with recurrent/persistent diarrhea and opportunistic infections that may lead to death; also at risk for graft-versus-host disease from maternal immunocompetent T-cells that crossed the placenta in utero**
  - **If patient continues to live without treatment, typical B-cell related infections will develop**
- **Diagnosis:** all patients have lymphopenia from birth, low-to-absent T-cells and absence of lymphocyte proliferative response to mitogens low-to-absent serum IGs and no antibodies after immunizations. The X-linked form has a low percentage of T and NK cells; autosomal recessive form more common in Europe (mutated forms in 12 genes). ADA deficiency affects primarily T-cell function (most severe lymphopenia from birth; second most common form; deletions of chromosome 20).
- **Treatment: stem cell transplantation** (HLA-identical or T-cell depleted half-matched parental); without it, most patients will die in first year but if diagnosed in first 3-4 months and treated, 94% will survive. The ADA form and X-linked have been treated with somatic gene therapy.

Combined immunodeficiency

Combined immunodeficiency is the **presence of low but not absent T-cell function and low but not absent antibodies;** patients survive longer but have failure-to-thrive and still die relatively early in life which are:

Wiskott-Aldrich syndrome

Wiskott-Aldrich Syndrome is an impaired humoral immune response and highly variable concentrations of the IGs with moderately reduced T-cells and variable mitogen responses.

- **Genetics: X-linked recessive** (Xp11.22-11.23); encodes a cytoplasmic protein restricted in expression to hematopoietic cell lines (WASP = Wiskott-Aldrich Syndrome Protein)
- **Clinical findings:** (1) thrombocytopenia presenting in neonatal period or early infancy most commonly with prolonged circumcision bleeding or bloody diarrhea, (2) atopic dermatitis, and (3) recurrent infections in first year of life (early encapsulated bacteria causing otitis, pneumonia, meningitis and sepsis, then later opportunistic infections)
- **Diagnosis:** clinical and molecular genetics; most common IG pattern is low IgM, high IgA and IgE and normal to slightly low IgG and variably reduced T-cells.
- **Treatment:** rare survival beyond adolescence (bleeding, infections and EBV-associated malignancies and autoimmune complications) without a **bone marrow transplant**

Ataxia-telangiectasia

Ataxia-telangiectasia is a moderately depressed response to T and B-cell mitogens, moderately reduced CD3 and CD4 T-cells with normal or increased percentages of CD8, T-helper cell and intrinsic B-cell defects, and hypoplastic thymus.

- **Genetics:** AT mutation (ATM) at 11.22-23
- **Clinical findings:** (1) ataxia evident with onset of walking and progresses until age 10-12 years when a wheelchair is needed (2) oculocutaneous telangiectasias develop at 3-6 years of age and (3) recurrent sinopulmonary infections most with common viruses and occasional fatal varicella; lymphoreticular malignancies and adenocarcinomas develop later; unaffected relatives also have increased incidence of malignancies
- **Treatment:** supportive care

Disorders of Phagocytic Function

Leukocyte adhesion deficiency

Leukocyte adhesion deficiency is a rare disorder of leukocyte function causing recurrent bacterial and fungal infections and **decreased inflammatory responses in the presence of neutrophilia (increased counts)**.

- **Genetics:** autosomal recessive with 3 types; affects neutrophil adhesion; mutation of 21q22.3 (results in decreased expression of β_2-integrin to the endothelial surface, exiting of neutrophils from the circulation and adhesion to microorganisms (which promotes phagocytosis and activation of NADPH oxidase)
- **Clinical findings:** infant with recurrent, **low-grade bacterial infections of the skin, large chronic oral ulcers with polymicrobes and severe gingivitis; respiratory tract and genital mucosa; delayed separation of the umbilical cord with omphalitis; typical signs of inflammation may be absent and there is no pus formation; most common organisms are *S. aureus*, gram-negatives and *Candida and Aspergillus***
- **Diagnosis: paucity of neutrophils in affected tissue but circulating neutrophil count is significantly elevated**; assessment of neutrophil and monocyte adherence, aggregation, chemotaxis and phagocytosis are all abnormal diagnosis confirmed with flow cytometry
- **Treatment:** early allogenic stem-cell transplantation for severe forms otherwise supportive care

Chronic granulomatous disease

Chronic granulomatous disease (CGD) is when neutrophils and monocytes phagocytize but cannot kill **catalase-positive microorganisms as a result of a defect in production of oxidative metabolites.**

- **Genetics/pathogenesis:** one **X-linked** and 3 autosomal recessive genes; most are **males** with X-linked inheritance; neutrophils do not produce **hydrogen peroxide, which usually acts as a substrate for myeloperoxidase** needed to oxidize halide to hypochlorous acid and chloramines that kill microbes; if organism is **catalase positive**, the organism's hydrogen peroxide is metabolized and the organism survives, **while catalase-negative organisms are killed**

- **Clinical findings:** variable age on onset and severity; **recurrent abscesses** (skin, lymph nodes, liver), pneumonia, osteomyelitis; most common pathogens are ***S. aureus*** and then *S. marcescens, B. cepacia**, Aspergillus and C. albicans**, Nocardia and Salmonella;* granuloma formation (due to abnormal accumulation of ingested material) and inflammatory processes are the hallmark (pyloric outlet obstruction, bladder or ureteral obstruction, rectal fistulae or granulomatous colitis
- **Diagnosis**: flow cytometry using **dihydrorhodamine 123 (DHR) to measure oxidant production through increased fluorescence when oxidized by hydrogen peroxide (has taken the place of the NBT);** identifying specific genetic subgroup is useful for genetic counseling and prenatal diagnosis
- **Treatment:** only cure is stem cell transplant; otherwise supportive care including interferon to reduce serious infections

Clinical Recall

Which of the following immune deficiencies is correctly matched to its treatment?

A. X-linked agammaglobulinemia: IVIG

B. DiGeorge syndrome: thyroid transplant

C. CVID: systemic steroids

D. Selective IgA deficiency: bone marrow transplant

E. Wiskott-Aldrich syndrome: treat infections as needed

Answer: A

OTHER IMMUNE DEFICIENCIES

Chédiak-Higashi Syndrome

- Autosomal recessive
- Abnormal secretory/storage granules lead to large and irregular seen in neutrophils
- Oculocutaneous albinism from birth, prolonged bleeding time, peripheral neuropathy, recurrent infections
- Bone marrow transplant or death from infection or lymphoproliferative-like disorder

Complement Deficiencies (Rare)

- Total hemolytic complement screens for most disease of the system; it depends on all 11 components of the classical system; alternative pathway activity (D and B factors) and properdin can be diagnosed with a different assay (AP_{50})
- All components are autosomal recessive or co-dominant, except for properdin deficiency which is X-linked recessive

- Decrease in both C3 and C4 suggests activation of the alternative pathway; this is most useful in distinguishing nephritis secondary to immune complex deposition from that due to nephritic factor
- Defect in complement function: recurrent angioedema, autoimmune disease, chronic nephritis, HUS, recurrent pyogenic infections, disseminated meningococcal or gonococcal infections or a second episode of bacteremia at any age; high incidence of pneumococcal and meningococcal infections
- The only significant one (in terms of numbers of people) is ineffective synthesis of active C1 inhibitor which produces hereditary angioedema.

Graft-Versus-Host Disease (GVHD)

- Major cause of morbidity and mortality after allogenic stem cell transplantation
- Caused by engraftment of immunocompetent donor lymphocytes in an immunocompromised host that shows histocompatibility differences with the donor lead to donor T-cell activation against recipient major or minor MHC antigens
- Acute GVHD: 2-5 weeks post-transplant; erythematous maculopapular rash, persistent anorexia, vomiting and/or diarrhea and abnormal liver enzymes and LFTs; primary prevention is with post-transplant immunosuppressive drugs and corticosteroids
- Chronic GVHD: develops or persists >3 months after transplant; major cause of non-relapse morbidity and mortality in long-term transplant survivors
  - Disorder of immune regulation: autoantibody production, increased collagen deposition and fibrosis and signs and symptoms of autoimmune disease

Disorders of the Eye 11

Learning Objectives

- ❑ Answer questions about congenital and acquired abnormalities of the eye structures
- ❑ Recognize and describe treatment approaches to periorbital versus orbital cellulitis

ABNORMALITIES OF THE EYE STRUCTURES

Pupils and Iris

- **Coloboma of iris**
  - Often autosomal dominant
  - Defect of lid, iris, lens, retina, or choroid
  - Always inferior—**keyhole appearance of iris; in lid, manifests as cleft**
  - **Possible CHARGE association**
- **Leukocoria—white reflex**
  - **Retinoblastoma**
  - **Cataract**
  - Retinopathy of prematurity
  - Retinal detachment
  - Larval granulomatosis

Lens

- Cataracts—opacity of the lens; most common etiologies:
  - Prematurity
  - Inheritance
  - Congenital rubella (occasionally other congenital infections)
  - Trisomies, other chromosomal defects
  - Drugs, trauma, toxins
- Ectopia lentis—instability or displacement of lens; edge of displaced lens may be visible in pupillary aperture
  - Differential:
    - **Trauma—most common**
    - Uveitis, congenital glaucoma, cataract, aniridia, tumor
    - Systemic causes: Marfan syndrome, homocystinuria, Ehlers-Danlos syndrome

Ocular Muscles

- **Strabismus**
  - Definition—Misalignment of the eyes from abnormal innervation of muscles
  - Diagnosis—**Hirschberg corneal light reflex**—most rapid and easily performed; **light reflex should be symmetric and slightly nasal to center of each pupil**
  - Patch the good eye to eliminate amblyopia, then eye muscle surgery
- Pseudostrabismus
  - Epicanthal folds and broad nasal bridge
  - Caused by unique facial characteristics of infant
  - Transient pseudostrabismus; common up to age 4 months

Conjunctiva

A 12-hour-old newborn is noted to have bilateral conjunctival injection, tearing, and some swelling of the left eyelid. Physical examination is otherwise normal.

Note

Chemical: first day

Gonorrhea: first week

Chlamydia: second week (most common)

Note

Congenital **nasolacrimal duct obstruction** (dacryostenosis)

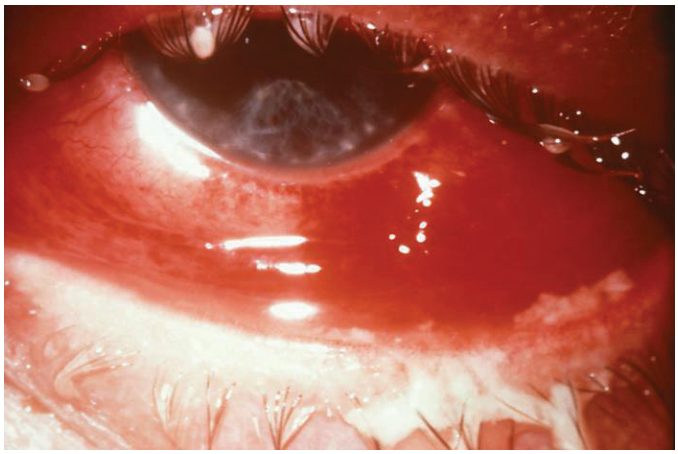
- Failure of canalization of duct as it enters the nose
- Excessive tears, **mucoid material** that is produced in the lacrimal sac, erythema
- Treatment—**nasolacrimal massage** 2–3×/day and warm water cleansing
- **Most resolve <1 year of age**

Note

Topical erythromycin *does not* prevent chlamydia conjunctivitis.

- **Ophthalmia neonatorum**
  - Redness, chemosis, edema of eyelids, purulent discharge
  - Causes:
    - Chemical conjunctivitis **most common in first 24 hours of life** (from silver nitrate and erythromycin)
    - *N. gonorrhea*—**2–5-day incubation**; may be delayed >5 days due to suppression from prophylactic eye treatment; mild inflammatory and serosanguineous discharge, then thick and purulent; complications are corneal **ulceration**, perforation, iridocyclitis
    - *C. trachomatis*—**5–14-day incubation; most common;** mild inflammation to severe swelling with purulent discharge; mainly **tarsal conjunctivae**; cornea rarely affected
  - **Diagnosis—Gram stain, culture, PCR (polymerase chain reaction) for chlamydia**
  - Treatment:
    - ***N. gonorrhea*: ceftriaxone × 1 dose IM + saline irrigation until clear**
    - **Chlamydia: erythromycin PO × 2 weeks + saline irrigation until clear (may prevent subsequent pneumonia)**
- **The red eye**
  - Bacterial conjunctivitis
    - General conjunctival hyperemia, edema, **mucopurulent exudate** (crusting of lids together), and eye discomfort
    - Unilateral or bilateral
    - *S. pneumonia, H. influenza* (non-typable), *S. aureus*, other strep
    - Treatment—warm compresses and **topical antibiotics**

- Viral conjunctivitis
  - **Watery discharge, bilateral, usually with URI**
  - Adenovirus, enterovirus
  - Epidemic keratoconjunctivitis = adenovirus type 8
  - Good hand-washing



phil.cdc.gov.

Figure 11-1. Purulent, Bacterial Conjunctivitis Secondary to Gonococcal Infection of the Eye

- Allergic
- Chemical
  - Household **cleaning substances**, sprays, smoke, smog
  - Extensive tissue damage, loss of sight
- Keratitis—**corneal** involvement
  - **H. simplex, adenovirus**, *S. pneumoniae, S. aureus*, *Pseudomonas*, chemicals
- Foreign bodies → corneal abrasion (pain, photophobia)
- Anterior uveitis = iridocyclitis (from ciliary body to iris)
- Periorbital versus orbital cellulitis
- Dacryocystitis (*S. aureus, H. influenza, S. pneumoniae*), dacryoadenitis (*S. aureus*, streptococci, CMV [cytomegalovirus], measles, EBV [Epstein-Barr virus], trauma)
- Treatment—underlying cause and topical steroids

Retina and Vitreous

- Retinopathy of prematurity (ROP)
  - **Prematurity, hyperoxia, and general illness**
  - From mild to severe progressive **vasoproliferative scarring** and blinding retinal detachment
  - Treatment—**bevacizumab or laser photocoagulation**

- Retinoblastoma
  - **Most common primary malignant intraocular tumor**
    - Recessive-suppressive gene—13q14 → family members need to be screened
  - Average age of diagnosis = 15 months for bilateral and 25 months for unilateral
    - **Rarely discovered at birth**
  - Initial sign in most = **leukocoria**
    - Appears as **white mass**
    - Second most common—**strabismus**
  - Diagnosis—**CT scan** to confirm; **no biopsy** (spreads easily)
  - Need to **consider enucleation—**radiation, chemotherapy, laser therapy, cryotherapy
  - Prognosis poor if extends into orbit or optic nerve

EYE INJURIES

Corneal Abrasions

- Symptoms—**pain, tearing**, photophobia, decreased vision
- Diagnosis—first anesthetize eye, then **fluorescein and blue-filtered light (Wood's lamp)**
- Treatment—**pain relief and topical antibiotics**

Foreign Body

Attempt gentle removal with irrigation or moist cotton-tipped applicator; if embedded body cannot be easily removed, refer immediately to an ophthalmologist.

PERIORBITAL VERSUS ORBITAL CELLULITIS

Periorbital Cellulitis

- Inflammation of **lids and periorbital tissue** without signs of true orbital involvement; insidious onset; low-grade fever; no toxicity
- Causes—**trauma, infected wound**, abscess of lid, **sinusitis, bacteremia** (***H. influenza* nontypeable,** *S. pneumoniae, S. aureus*)
- May be first sign of sinusitis that may progress to orbital cellulitis
  - Physical exam: inflammation with intact eye movements; normal vision; no proptosis
- Diagnosis—clinical (blood culture unlikely to be positive)
- Treatment—**oral or IV (depending on severity) antibiotics (cover for *S. aureus* and gram-positive resistant strains)**

Orbital Cellulitis

A 7-year-old boy presents with swelling around the eye 2 days after suffering an insect bite to the eyelid. There is edema, erythema, and proptosis of the eye. Marked limitation of eye movements is noted. He has a low-grade fever.

- Infection of orbital tissue including subperiosteal and retrobulbar abscesses
- Physical examination
  - Ophthalmoplegia (**eyeball does not move**)
  - Chemosis
  - Inflammation
  - Proptosis
- Toxicity, fever, leukocytosis, acute onset
- Causes: **paranasal sinusitis, direct infection from wound, bacteremia**
- Organisms **nontypeable *H. influenza, S. aureus*, beta hemolytic strep**, ***S. pneumoniae***, anaerobes
- Diagnosis—CT scan with contrast of orbits and surrounding area (**best initial test**)
- Treatment—**Intravenous antibiotics (again, cover for *S. aureus*) and may require sinus and/or orbital drainage** (will give you culture and sensitivities) if no improvement

Clinical Recall

A 5-day-old newborn boy presents with thick, purulent discharge of the right eye and evidence of a corneal ulcer. What is the likely etiology?

A. Syphilis

B. Chlamydia

C. HIV

D. Gonorrhea

E. Silver nitrate

Answer: D

Disorders of the Ear, Nose, and Throat

12

Learning Objectives

- ❑ Describe diagnosis and treatment of disorders of the ears, nose, and throat in childhood
- ❑ Demonstrate understanding of disorders of the oral cavity

EARS

External Ear

Otitis externa (swimmer's ear)

- Normal flora of external canal includes ***Pseudomonas aeruginosa*** **(most common cause)**, ***S. aureus*** **(second most common cause)**, coagulase-negative *Staphylococcus*, diphtheroids, *Micrococcus* spp., and viridans streptococci
- Causes—excessive wetness, dryness, skin pathology, or trauma
- Symptoms—**significant pain** (especially with **manipulation of outer ear**), conductive hearing loss
- Findings—edema, erythema, **thick otorrhea,** preauricular nodes
- Malignant external otitis is invasive to temporal bone and skull base, with facial paralysis, vertigo, other cranial nerve abnormalities; **requires immediate culture, IV antibiotics, and imaging (CT scan) → may need surgery**
- Treatment—**topical otic preparations ± corticosteroids**
- Prevention—**earplugs, thorough drying of canal, and 2% acetic acid after getting wet**

Middle Ear

Otitis media (OM)

A 4-year-old child is seen in the office with a 3-day history of fever and cold symptoms and now complains of right ear pain. Physical examination is remarkable for a bulging tympanic membrane with loss of light reflex and landmarks.

- Acute, suppurative otitis media; accompanied by a variable degree of hearing loss (20–30 dB)

Clinical Correlate

Otitis Media Correlated Factors

- Commonly first 2 yrs of life; boys > girls; Native Americans/Inuit; low SES
- Heritable genetic component
- Protective effect of breast milk vs. formula
- Positive correlation to both tobacco smoke and exposure to other children
- Season: cold weather
- Congenital anomalies: more with palatal clefts, other craniofacial anomalies, and Down syndrome

Note

Abnormal Exam Findings

Purulent otorrhea: sign of otitis externa, otitis media with perforation and/or drainage from middle ear through tympanostomy tube

Bulging TM: increased middle ear pressure with pus or effusion in middle ear

TM retraction: negative middle ear pressure (more rapid diffusion of air from middle ear cavity than its replacement via the eustachian tube)

Other findings for an effusion: bubbles, air-fluid level seen behind TM

- Etiology
  - Bacterial (up to 75%): ***S. pneumoniae*** (40%); **nontypeable *H. influenzae*** (25–30%); ***Moraxella catarrhalis*** (10–15%)
  - Other 5%: Group A strep, *S. aureus*, gram negatives (neonates and hospitalized very young infants), respiratory viruses (rhinovirus, RSV most often)
- Pathogenesis
  - Interruption of normal eustachian tube function (ventilation) by obstruction → inflammatory response → middle ear effusion → infection; most with URI
  - Shorter and more horizontal orientation of tube in infants and young children allows for reflux from pharynx (and in certain ethnic groups and syndromes)
- Clinical findings highly variable
  - Symptoms: ear pain, fever, purulent otorrhea (ruptured tympanic membrane), irritability, or no symptoms
  - Pneumatic otoscopy: fullness/bulging or extreme retraction, intense erythema (otherwise erythema may be from crying, fever, sneezing; erythema alone is insufficient unless intense), some degree of opacity (underlying effusion)
  - Mobility is the most sensitive and specific factor to determine presence of a middle ear effusion (pneumatic otoscopy)
- Diagnosis: must have **acute onset, tympanic membrane inflammation, middle ear effusion**
- Treatment: advisable to use routine antimicrobial treatment especially for age <2 years or those systemically ill, with severe infection, or with history of recurrent acute otitis media.
  - Pain relief is essential: acetaminophen, NSAIDs (except acetylsalicylic acid because of risk of Reye syndrome)
  - **First-line drug of choice = amoxicillin (high dose)**
  - **Alternate first-line drug or history of penicillin allergy = azithromycin**
  - In some patients age >2 years with no high fever or severe pain, observation and reevaluation in 2-3 days are acceptable; if no improvement, start antibiotics.
  - Duration: 10 days; shorter if mild, older child
  - Follow up: within days for young infants, continued pain or severe; otherwise 8–12 wks if age <2 yrs or ≥2 yrs and with language/learning problems (sustained improvement seen in TM)
  - **Second-line drugs—if continued pain after 2–3 days**
    - Amoxicillin-clavulanic acid (effective against β-lactamase producing strains)
    - Cefuroxime axetil (unpalatable, low acceptance)
    - **IM ceftriaxone** (may need repeat 1–2×; for severe infection if oral not possible) **if patient is not taking/tolerating oral medications**
    - Also maybe cefdinir (very palatable, shorter duration)
    - If **clinical response to good second-line drug is unsatisfactory**, perform myringotomy or tympanocentesis

Otitis media with effusion (OME)

- Generally after repeated infections with insufficient time for effusion to resolve
- **Fullness is absent or slight or TM retracted; no or very little erythema**

- Treatment
  - Monthly evaluation
  - Assess hearing if effusion >3 months; most resolve without problems
  - **Recent studies suggest that in otherwise healthy children an effusion up to 9 months in both ears during first 3 years of life poses no developmental risks at 3–4 years of life.**
  - **Routine antibiotic prophylaxis is *not* recommended.**
  - **Tympanostomy tubes**
    - **For children with bilateral OME and impaired hearing for >3 months; prolonged unilateral or bilateral OME with symptoms (school or behavioral problems, vestibular, ear discomfort); or prolonged OME in cases of risk for developmental difficulties (Down syndrome, craniofacial disorders, developmental disorders).**
    - Likelihood that middle ear ventilation will be sustained for at least as long as tubes remain in (average 12 months)
- Complications
  - Acute mastoiditis: **displacement of pinna** inferiorly and anteriorly and inflammation of posterior auricular area; pain on percussion of mastoid process
    - Diagnosis: when suspected or diagnosed clinically, perform CT of temporal bone
    - Treatment: **myringotomy and IV antibiotics** (*S. pneumoniae*, nontypeable *H. influenzae, P. aeruginosa*); if bone destruction, intravenous antibiotics and mastoidectomy
  - **Acquired cholesteatoma** = cyst-like growth within middle ear or temporal bone; lined by keratinized, stratified squamous epithelium
    - Most with long-standing chronic otitis media
    - **Progressively expands:** bony resorption and intracranially; life-threatening
    - **Discrete, white opacity of eardrum** through a defect in TM or persistent malodorous ear discharge
    - **CT scan** to define presence and extent
    - Treatment: **tympanomastoid surgery**

Clinical Recall

A 5-year-old boy with a history of recurrent acute otitis media and penicillin allergy receives a diagnosis of otitis media with effusion. What is the next step?

A. Prescribe amoxicillin

B. No antibiotics are needed

C. Refer for tympanostomy tube placement

D. Prescribe azithromycin

E. Admit for IV antibiotics

Answer: D

ORAL CAVITY

Cleft Lip and Palate

- Most are **multifactorial** inheritance; also **autosomal dominant in families (most with isolated cleft palate)**
- Clefts are highest among Asians, lowest among African descent
- **Increase in other malformations with isolated cleft palate**
- **Most important early issue is feeding (special nipple needed)**
- Complications—increased risk of otitis media, hearing loss, speech problems
- Treatment—surgical correction
  - Lip at 3 months of age
  - Palate at <1 year

NOSE AND THROAT

Nose

Choanal atresia

A newborn is noted to be cyanotic in the wellborn nursery. On stimulation, he cries and becomes pink again. The nurse has difficulty passing a catheter through the nose.

- Unilateral or bilateral bony (most) or membranous septum between nose and pharynx
  - Half have other anomalies (**CHARGE** association)
  - Unilateral—asymptomatic for long time until first URI, then persistent nasal discharge with obstruction
  - Bilateral—**typical pattern of cyanosis while trying to breathe through nose, then becoming pink with crying**; if can breathe through mouth, will have problems while feeding
- Diagnosis
  - Inability to pass catheter 3–4 cm into nasopharynx
  - Fiberoptic rhinoscopy
  - Best way to delineate anatomy is CT scan
- Treatment
  - Establish oral airway, possible intubation
  - Transnasal repair with stent(s)

Foreign body

- Any small object
- Clinical—unilateral **purulent, malodorous bloody discharge**
- Diagnosis—may be seen with nasal speculum or otoscope; lateral skull film if radiopaque (may have been pushed back, embedded in granulation tissue)
- Treatment—if cannot easily remove with needle-nose forceps, refer to ENT

Epistaxis

An 8-year-old child has repeated episodes of nosebleeds. Past history, family history, and physical examination are unremarkable.

- Common in childhood; decreases with puberty
- Most common area—**anterior septum** (Kiesselbach plexus), prone to exposure
- Etiology
  - **Digital trauma** (nose picking; most common)
  - **Dry air (especially winter)**
  - **Allergy**
  - **Inflammation (especially with URI)**
  - **Nasal steroid sprays**
  - Severe GERD in young infants
  - Congenital vascular anomalies
  - Clotting disorders, hypertension
- Treatment—most stop spontaneously
  - Compress nares, upright, head forward; cold compress
  - If this does not work, then **local oxymetazoline or phenylephrine**
  - If this does not work, then **anterior nasal packing**; if it appears to be coming posteriorly, need **posterior nasal packing**
  - If bleeding site identified, **cautery**
  - Use humidifier, saline drops, petrolatum for prevention

Polyps

- Benign pedunculated tumors from chronically inflamed nasal mucosa
  - Usually from ethmoid sinus external to middle meatus
- **Most common cause is cystic fibrosis—suspect in any child <12 years old with polyp; EVEN in absence of other typical symptoms**
- May also be associated with the Samter triad (polyps, aspirin sensitivity, asthma)
- Presents with **obstruction** → hyponasal speech and mouth breathing; may have profuse mucopurulent rhinorrhea
- Examination—generally glistening, gray, grape-like masses
- Treatment—**intranasal steroids/systemic steroids may provide some shrinkage (helpful in CF);** remove surgically if complete obstruction, uncontrolled rhinorrhea, or nose deformity.

Sinusitis

- Acute—viral versus bacterial
- Most with URI—most viral, self-limited; up to 2% complicated by bacterial sinusitis
- Sinus development
  - Ethmoid and maxillary present at birth, but only **ethmoid is pneumatized**
  - Sphenoid present by 5 years
  - Frontal begins at 7–8 years and not completely developed until adolescence

Note

The same organisms that are responsible for AOM are also implicated in sinusitis.

- Etiology—***S. pneumonia*, nontypeable *H. influenzae, M. catarrhalis; S. aureus* in chronic cases**
  - May occur at **any age**
  - Predisposed with URI, allergy, cigarette smoke exposure
  - Chronic—immune deficiency, CF, ciliary dysfunction, abnormality of phagocytic function, GERD, cleft palate, nasal polyps, nasal foreign body
- Pathophysiology—fluid in sinuses during most URIs from nose blowing. Inflammation and edema may block sinus drainage and impair clearance of bacteria.
- Clinical features
  - **Nonspecific complaints—nasal congestion, discharge, fever, cough**
  - Less commonly—bad breath, decreased sense of smell, periorbital edema headache, face pain
  - Sinus tenderness only in adolescents and adults; exam mostly shows mild erythema and swelling of nasal mucosa and discharge
- Diagnosis—**entirely historical and clinical presentation (evidence-based)**
  - **Persistent URI symptoms without improvement for at least 10 days**
  - **Severe respiratory symptoms with purulent discharge and temperature at least 38.9 C (102 F) for at least 3 consecutive days**
    - Only accurate method to distinguish viral versus bacterial is sinus aspirate and culture, but this is NOT done routinely
    - Sinus films/CT scans—show mucosal thickening, opacification, air-fluid levels but does not distinguish viral versus bacterial
- Treatment
  - Initial—amoxicillin (adequate for majority)
  - Alternative—cefuroxime axetil, cefpodoxime, azithromycin
  - Treat 7 days past improvement
  - If still does not work—to ENT (maxillary sinus aspirate)

Throat

Acute pharyngitis

An 8-year-old girl complains of acute sore throat of 2 days' duration, accompanied by fever and mild abdominal pain. Physical examination reveals enlarged, erythematous tonsils with exudate and enlarged, slightly tender cervical lymph nodes.

- Viruses versus group A beta-hemolytic strep (GABHS)
- Viral—typical winter and spring; close contact
- GABHS—**uncommon <2–3 years of age**; increased incidence in childhood, then decreases in adolescence; **all year long** (but most in cold months)
- Clinical presentation
  - Strep pharyngitis
    - **Rapid onset**
    - **Severe sore throat and fever**

    - **Headache and gastrointestinal symptoms frequently**
    - **Exam—red pharynx, tonsillar enlargement with yellow, blood-tinged exudate, petechiae on palate and posterior pharynx, strawberry tongue, red swollen uvula, increased and tender anterior cervical nodes**
  - Scarlet fever—from GABHS that produce one of 3 streptococcal pyogenic exotoxins (SPE A, B, C); **exposure to each confers a specific immunity to that toxin, so a person can have scarlet fever up to 3 times**
    - Findings of pharyngitis plus **circumoral pallor**
    - **Red, finely papular erythematous rash diffusely that feels like sandpaper**
    - Pastia lines in intertriginous areas
  - Viral—more gradual; with typical URI symptoms; erythematous pharynx, no pus
    - Pharyngoconjunctival fever (adenovirus)
    - **Coxsackie**:
      - Herpangina—small 1–2 mm vesicles and ulcers on posterior pharynx
      - Acute lymphonodular pharyngitis—small 3–6 mm yellowish-white nodules on posterior pharynx with lymphadenopathy
      - **Hand-foot-mouth disease—inflamed oropharynx with scattered vesicles on tongue, buccal mucosa, gingiva, lips, and posterior pharynx → ulcerate; also on hands and feet and buttocks; tend to be painful**
- Diagnosis of strep
  - First—**rapid strep test; if positive, do not need throat culture**
    - **But must confirm a negative rapid test with cultures if clinical suspicion is high**
- Treatment—early treatment only hastens recovery by 12–24 hours **but prevents acute rheumatic fever if treated within 9 days of illness**
  - **Penicillin**
  - **Allergy—erythromycin**
- Complications
  - Retropharyngeal and lateral pharyngeal abscess—deep nodes in neck; infection from extension of localized infection of oropharynx
    - Clinical—nonspecific—fever, irritability, decreased oral intake, **neck stiffness, torticollis, refusal to move neck, muffled voice**
    - **Examination—bulging of posterior or lateral pharyngeal wall**
    - Soft tissue neck film with head extended may show increase width
    - Definitive diagnosis—incision and drainage, **C and S—most polymicrobial (GABHS, anaerobes, *S. aureus*)**
    - **Treatment**
      - Intravenous antibiotics ± surgical drainage
      - **Third-generation cephalosporin plus ampicillin/sulbactam or clindamycin**
      - **Surgical drainage needed if respiratory distress or failure to improve**
  - Peritonsillar abscess—bacterial invasion through capsule of tonsil
    - Typical presentation—adolescent with recurrent history of acute pharyngotonsillitis
    - Sore throat, fever, dysphagia, trismus

Note

Causes of Cervical Lymphadenitis

- Infections
  - Viral/bacterial pharyngitis
  - Cat scratch disease
  - Tb/atypical mycobacteria
  - Mumps
  - Thyroglossal duct cyst
  - Branchial cleft cyst
- Cystic hygroma
- Tumors (rare)

- Examination—**asymmetric tonsillar bulge with displacement of uvula away from the affected side is diagnostic**
- GABHS + mixed oropharyngeal anaerobes
- Treatment
  - Antibiotics and **needle aspiration**
  - **Incision and drainage**
  - **Tonsillectomy if recurrence or complications (rupture with aspiration)**

Clinical Recall

A 7-year-old girl presents with fever and sore throat. Exam reveals tonsillar erythema and exudates. Rapid strep test is positive. What is the next step?

A. Swab the throat for culture

B. Prescribe penicillin

C. Obtain a blood culture

D. Advise rest and fluids with follow-up as needed

E. Perform a second rapid strep test for confirmation

Answer: B

Cardiology 13

Learning Objectives

- ❑ Demonstrate understanding of the pediatric cardiac evaluation
- ❑ Categorize disorders in which left-to-right shunt, right-to-left shunt, or hypertension occurs
- ❑ Recognize stenotic, regurgitant, and mixed disorders

CARDIAC EVALUATION AND CONGENITAL HEART LESIONS

Children do not present with the typical features of congestive heart failure as seen in adults. Age is very important when assessing the child.

- Infants:
  - Feeding difficulties
  - Easily fatigued
  - Sweating while feeding
  - Rapid respirations
- Older children:
  - Shortness of breath
  - Dyspnea on exertion
- Physical examination
  - Need to refer to normal heart and respiratory rates for ages to determine tachycardia and tachypnea.
  - Height and weight should be assessed to determine proper growth.
  - Always get upper and lower extremity blood pressures and pulses.
  - Hepatosplenomegaly suggests right-sided heart failure.
  - Rales on auscultation may indicate pulmonary edema and left-sided heart failure.
  - Cyanosis and clubbing result from hypoxia.

Note

Orthopnea and nocturnal dyspnea are **rare** findings in children.

Table 13-1. Heart Murmur Gradation

Grade	Quality
1	Soft, difficult to hear
2	Easily heard
3	Louder but no thrill
4	Associated with thrill
5	Thrill; audible with edge of stethoscope
6	Thrill; audible with stethoscope just off chest

- Diagnostic tests
  - Chest radiograph—evaluate heart size, lung fields, ribs for notching, position of great vessels
  - Electrocardiogram
  - **Echocardiography—definitive diagnosis**
  - Other—MRI, cardiac catheterization, angiography, exercise testing
- Embryology—knowledge of cardiac embryology is helpful for understanding congenital cardiac lesions, their presentations, symptoms, and treatment.

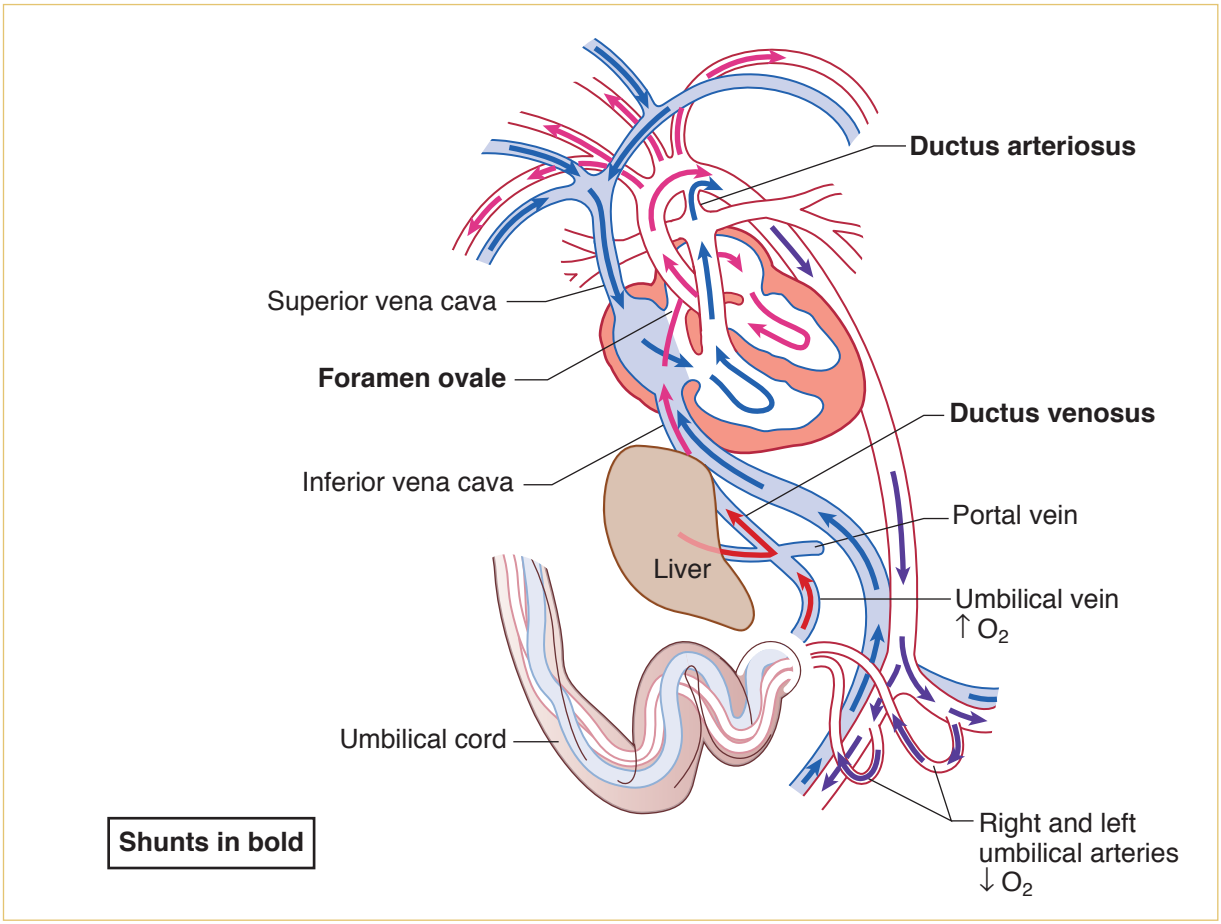


Figure 13-1. Fetal Circulation

PEDIATRIC HEART SOUNDS AND INNOCENT MURMURS

Heart Sounds

First heart sound (S1)

- Closure of mitral and tricuspid valves (MV, TV)
- High pitch, but lower pitch and greater intensity compared to S2
- Usually no discernible splitting of S1 but in completely normal child, a split S1 represents asynchronous closure of the 2 valves (20–30 msec difference); however, what sounds like a split S1 but does not represent pathology:
  - Split S1 best heard at apex or right upper sternal border; click (opening of stenotic valve, slightly later than a split S1) may be heard in aortic stenosis
  - Apical mid systolic click of mitral valve prolapse
  - At upper left sternal border, a click may be heard from pulmonic valve stenosis; compared to aortic stenosis, this changes with respiration (with inspiration, venous return is increased, thus causing the abnormal pulmonary valve to float superiorly after which the click softens or disappears)
  - Tricuspid valve abnormalities (e.g., Ebstein anomaly) may cause billowing of the leaflets and result in multiple clicks
- S1 may be inaudible at the lower left sternal border mostly due to sounds that obscure the closure of the MV and TV, e.g., in VSD, PDA, mitral or tricuspid regurgitation and severe right ventricular outflow tract obstruction. Therefore, if the **first heart sound is not heard at the lower left sternal border, there is most likely a congenital heart defect, and there will be other clinical and auscultatory findings.**

Second heart sound (S2)

- Closure of pulmonary and aortic valves (PV, AV), which close simultaneously on exhalation and a single heart sound is best heard with diaphragm at the upper left sternal border
  - **Wider splitting of S2 on inspiration is related not only to increased venous return but also to pressures in the aorta and pulmonary artery (PA) (it is significantly higher in the Ao than in the PA, so Ao valve closes first)**
- **Wider than normal splitting will occur with any lesion that allows more blood to traverse the PV compared to normal**
  - Increased splitting of S2 may be fixed with respect to respiration if there is increased volume and hence pressure in the right atrium (e.g., ASD); otherwise, it will continue to vary with respiration; may also hear fixed splitting with a right bundle branch block
- **Loud single S2**: heard with PA hypertension (increased pressure closing the PV causes early closure of the anterior semilunar valve resulting in a loud single S2)
  - In D-transposition, the AV is anterior and to the right of the PV, which overwhelms the sound from the PV, so one hears a loud single S2; in truncus arteriosus, there is only 1 valve so there is a single S2

Third heart sound (S3)

- Hear **early in diastole**; creates a gallop rhythm with S1 + S2; very low frequency and is best heard with bell of the stethoscope at cardiac apex; asking patient to lie on left side may increase intensity of S3
- **On occasion may be heard normally in children with no pathology:** in older people, it represents the presence of CHF or other volume overload and is caused by sudden deceleration of blood flow into LV from the LA

Fourth heart sound (S4)

- Occurs in **late diastole, just prior to S1 (presystolic) and is produced by a decrease in compliance (increased stiffness) of the LV**
- Low frequency (lower than S3) and best heard with bell of the stethoscope pressed lightly against the skin
- Summation gallop rhythm (S3 + S4) may be found with myocarditis or a cardiomyopathy (combination of volume overload and noncompliant ventricle)

Clinical Recall

A medical student is performing a physical exam on an infant. Cardiac auscultation reveals a loud single S2. What congenital anomaly does the infant likely have?

A. Atrial septal defect

B. Patent ductus arteriosus

C. Ventricular septal defect

D. Ebstein anomaly

E. D-transposition

Answer: E

Innocent Murmurs

Peripheral pulmonic stenosis

- **Normal finding age 6 weeks to 1 year**
- Generated by blood flowing into the lungs due to (1) pulmonary arteries, which have limited blood flow in utero and are therefore small with significantly increased blood flow after birth (turbulence from RV blood flowing through these arteries) and (2) increasing cardiac output associated with declining [Hgb] over the first weeks of life (physiologic anemia)
- Normal infant with normal S1, then grade 1-2 systolic ejection murmur at the upper sternal border and radiating bilaterally into the axillae; then, normal splitting of S2

Still's murmur

- Commonly heard first at **age 3–5 years**
- Represents turbulence or vibrations in either ventricle; child is healthy and asymptomatic

- Precordial activity is normal, as are S1 and S2; the murmur is typically low-pitched (bell of stethoscope), musical-quality and often radiates throughout the precordium.
- Murmur is **loudest while supine (greater blood flow) and decreases sitting or standing—opposite to the finding of HOCM.** Also increases with fever or exercise (hyperdynamic states).

Venous hum

- Only diastolic murmur that is **not** pathological; **represents blood flow returning from the head and flowing from SVC into the RA**
- Described as "whooshing" sound (like holding a seashell to your ear at the ocean); is a **continuous murmur**
  - Best heard in sitting position with head in the neutral position
  - **Murmur becomes softer or disappears while in supine, with slight pressure to the right side of the neck or turning head to opposite side**

Aortic outflow murmur

- Heard **in adolescents and young adults** (especially athletes, due to lower resting heart rate and therefore larger stroke volume
- Best heard in upper right sternal border; represents blood flow in LV outflow tract (**without a click, as there is in aortic stenosis**)
- Precordial activity is normal, S1 and S2 are normal, the murmur is grade 1-2 ejection
  - Going from **supine to sitting or standing decreases the murmur** (again, opposite to HOCM)

Congenital Heart Disease

In most cases, diagnosis usually made by age 1 month. Murmurs may not be heard in early life because of increased pulmonary vascular resistance (from fetal to neonatal transition physiology).

- Etiology
  - Most are unknown
  - Associated with teratogens, such as alcohol and rubella
  - Genetic predisposition—trisomies; Marfan, Noonan, DiGeorge syndromes (typically non-Mendelian)
- Classification

Table 13-2. Congenital Heart Disease

	Shunting			
Regurgitant	**Stenotic**	**Right → Left**	**Left → Right**	**Mixing**
MVP	Aortic stenosis	Tetralogy of Fallot	Patent ductus	Truncus arteriosus
PI, AI	Pulmonic stenosis	Ebstein anomaly	Ventricular septal defect	TAPVR
MI, TI	Coarctation of the aorta	Tricuspid atresia	Atrial septal defect, endocardial cushion defect	HLH, transposition of the great vessels

Definition of abbreviations: TAPVR *total anomalous pulmonary venous return*; HLH hypoplastic left heart; MVP mitral valve prolapse; PI pulmonic insufficiency; AI aortic insufficiency; MI mitral insufficiency; TI tricuspid insufficiency

Note

Eisenmenger Syndrome

- Transformation of any untreated left-to-right shunt into a bidirectional or right-to-left shunt
- Characterized by cyanosis
- Results from high pulmonary blood flow, causing medial hypertrophy of pulmonary vessels and increased pulmonary vascular resistance, resulting in pulmonary arterial hypertension and partial flow reversal

LEFT TO RIGHT SHUNTS

Ventricular Septal Defect (VSD)

A 3-month-old child presents with poor feeding, poor weight gain, and tachypnea. Physical examination reveals a harsh, pansystolic 3/6 murmur at the left lower sternal border, and hepatomegaly.

- **Most common** congenital heart lesion
- Most are **membranous**
- Shunt determined by **ratio of PVR to SVR**
  - **As PVR falls in first few weeks of life, shunt increases**
  - When PVR>SVR, **Eisenmenger** syndrome (must **not be allowed** to happen)
- Clinical findings
  - Asymptomatic if small defect with normal pulmonary artery pressure (most); large defect—**dyspnea, feeding difficulties, poor growth, sweating, pulmonary infection, heart failure**
  - Harsh holosystolic **murmur** over lower left sternal border ± thrill; S2 widely split and varies with respiration
  - With hemodynamically significant lesions, also a low-pitched diastolic rumble across the mitral valve heard best at the apex (increased diastolic flow leads to significant turbulence, which causes the murmur)

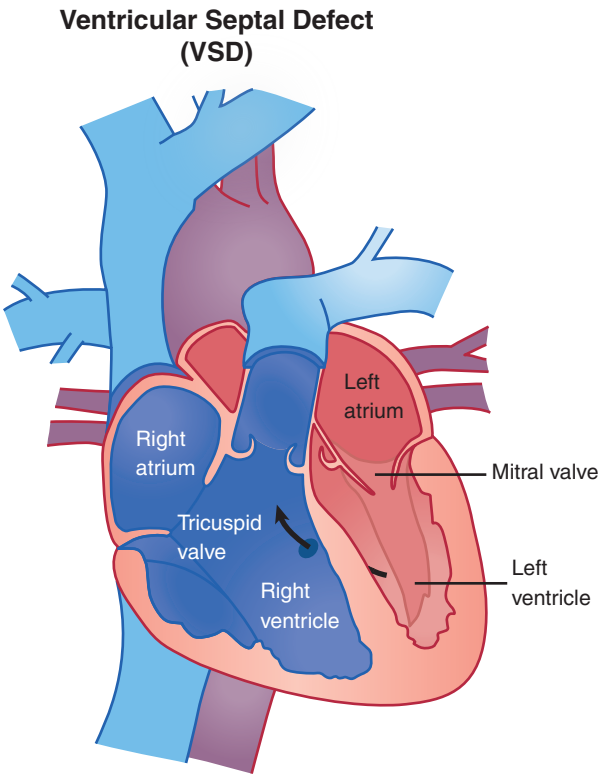
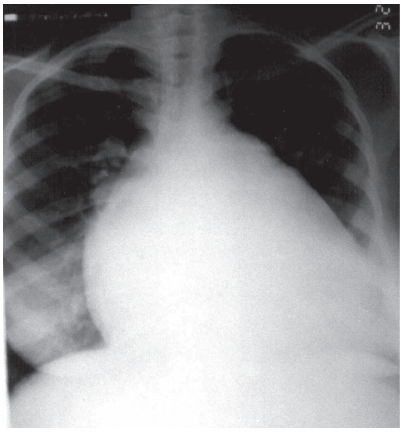


Figure 13-2. Ventricular Septal Defect

- Diagnosis
  - Chest x-ray: large heart, pulmonary edema
  - EKG: LVH early on, if no signs of dyspnea and increased RV pressure; if left unchecked, PA pressures and RV pressures will increase
  - Echocardiogram is definitive
- Treatment
  - Small **muscular VSD more likely to close in first 1–2 years than membranous**
  - Less common for moderate to large to close → medical treatment for heart failure (**control failure and prevent pulmonary vascular disease**)
  - **Surgery in first year**; indications:
    - Failure to thrive or unable to be corrected medically
    - Infants at 6–12 months with large defects and pulmonary artery hypertension
    - More than 24 months of age with Qp:Qs >2:1 (shunt fraction)



Courtesy of Tom D. Thacher, M.D.

Figure 13-3. Cardiomegaly Due to Ventricular Septal Defect

- Complications
  - Large defects lead to heart failure, failure to thrive
  - Endocarditis
  - Pulmonary hypertension

Atrial Septal Defect (ASD)

- Ostium secundum defect **most common** (in region of fossa ovalis)
- Clinical
  - **Few symptoms early in life** because of structure of low-flow, left-to-right shunt
  - In older children, often with large defects; varying degrees of exercise intolerance
  - With hemodynamically significant lesions, also a low-pitched diastolic rumble across the tricuspid valve heard best at the lower sternum

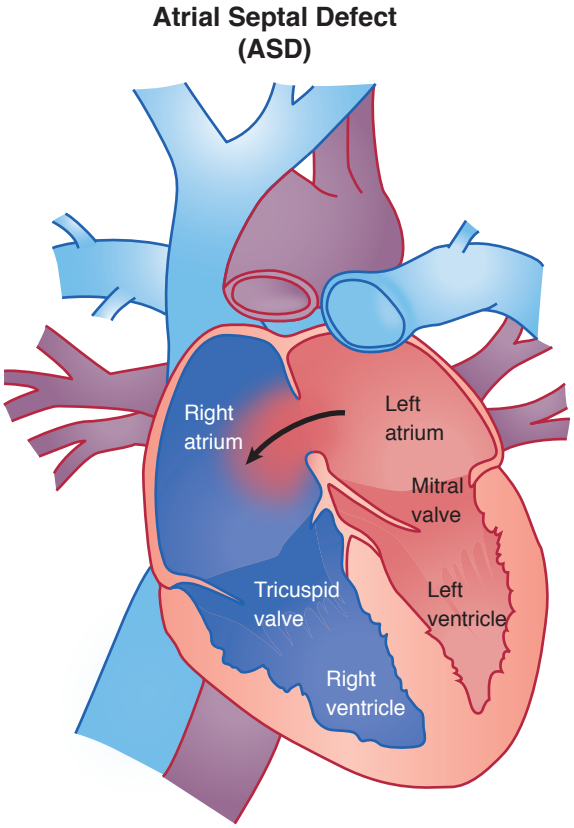


Figure 13-4. Atrial Septal Defect

- Physical examination
  - **Wide fixed splitting of S2**
  - Systolic ejection murmur along left mid to upper sternal border (from increased pulmonary flow)
- Diagnosis
  - Chest x-ray—varying heart enlargement (right ventricular and right atrial); increased pulmonary vessel markings, edema
  - EKG—**right-axis deviation and RVH**
  - Echocardiogram definitive
- Treatment
  - Most in term infants close spontaneously; **symptoms often do not appear until third decade**
  - **Surgery or transcatheter device closure for all symptomatic patients or 2:1 shunt**
- Complications
  - Dysrhythmia
  - Low-flow lesion; does not require endocarditis prophylaxis

Endocardial Cushion Defect

- Pathophysiology
  - When both ASDs and VSDs occur, which are contiguous, and the atrioventricular valves are abnormal
  - Left-to-right shunt at both atrial and ventricular levels; some right-to-left shunting with desaturation (**mild, intermittent cyanosis**)
  - Atrioventricular valve insufficiency → increase volume load on one or both ventricles; **early heart failure, infections, minimal cyanosis, hepatomegaly, and failure to thrive**
- Physical examination
  - Heart failure early in infancy (hepatomegaly, failure to thrive)
  - Eisenmenger physiology occurs earlier (due to increased ejection of blood from the large RV chamber into the narrow infundibulum)
  - Moderate-to-severe increase in heart size with hyperdynamic precordium (**precordial bulge and lift**)
  - **Widely fixed split S2** (like an isolated ASD)
  - **Pulmonary systolic ejection murmur, low-pitched diastolic rumble at left sternal border and xiphoid,** representing increased diastolic flow across both the MV and TV
- Diagnostic tests
  - Chest x-ray—significant cardiomegaly, increased pulmonary artery and pulmonary blood flow and edema
  - EKG—signs of biventricular hypertrophy, right atrial enlargement, superior QRS axis
  - Echocardiogram (gold standard)
- Treatment—surgery more difficult with heart failure and pulmonary hypertension (increased pulmonary artery pressure by 6–12 months of age); **must be performed in infancy**
- Complications
  - Without surgery—death from heart failure
  - With surgery—arrhythmias, congenital heart block

Note

Patients with trisomy 21 are at a higher risk for endocardial cushion defects.

Patent Ductus Arteriosus (PDA)

- Results when the ductus arteriosus fails to close; this leads to blood flow from the aorta to the pulmonary artery
- Risk factors
  - **More common in girls** by 2:1
  - Associated with **maternal rubella infection**
  - Common in **premature infants** (developmental, not heart disease)
- Presentation
  - If small—possibly no symptoms
  - If large—heart failure, a wide pulse pressure, bounding arterial pulses, characteristic sound of "machinery"

Note

If a PDA persists beyond the first week of life, it is unlikely to close spontaneously.

- Diagnostic tests
  - Chest x-ray—increased pulmonary artery with increased pulmonary markings and edema; moderate-to-large heart size
  - EKG—left ventricular hypertrophy
  - Echocardiogram—increased left atrium to aortic root; ductal flow, especially in diastole
- Treatment
  - May close spontaneously
  - Indomethacin (preterm infants)
  - Surgical closure
- Complications
  - Congestive heart failure
  - Infective endocarditis

STENOTIC LESIONS

Pulmonic Stenosis

Note

Pulmonic stenosis as a result of valve dysplasia is the common defect in **Noonan syndrome** (12q24.1; autosomal dominant; boys and girls with Turner phenotype).

Pulmonic stenosis (either valve or branched artery) is common in **Alagille syndrome** (arteriohepatic dysplasia).

- Pathophysiology
  - Deformed cusps → open incompletely during systole; obstruction to right ventricular outflow → increased systemic pressure and wall stress → **right ventricular hypertrophy (depends on severity of pulmonary stenosis)**
  - **Arterial saturation normal unless ASD or VSD is present with R → L shunt**
  - Neonate with severe pulmonary stenosis = critical pulmonary stenosis = R → L shunt via foramen ovale
- Physical examination
  - Heart failure only in severe cases, most in first month of life
  - Mild cases—normal life, usually no progression
  - **Moderate to severe**—increasing gradient with growth: **signs of right ventricular failure** (hepatomegaly, peripheral edema, exercise intolerance)
  - **Pulmonary ejection click** after S1 in left upper sternal border and normal S2 (in mild); relatively **short, low-to-medium–pitched SEM** over pulmonic area radiating to both lung fields
- Diagnosis
  - EKG—**right ventricular hypertrophy in moderate to severe**; tall, spiked P-waves; right atrial enlargement (RAE)
  - Chest x-ray—**poststenotic dilatation of pulmonary artery;** normal-to-increased heart size (right ventricle) and **decreasing pulmonary vascularity**
  - Echocardiogram (gold standard)
- Complications
  - Heart failure
  - Endocarditis (lower risk)
  - Secondary subvalvular muscular and fibrous hypertrophy
- Treatment
  - Moderate to severe—**balloon valvuloplasty** initially; may need surgery
  - Neonate with **critical pulmonary stenosis—emergent surgery**

Aortic Stenosis

- Most are **bicuspid aortic valve**—usually asymptomatic in children
- Supravalvular stenosis (least common form)—sporadic, familial, or with Williams syndrome (intellectual disability, elfin facies, heart disease, idiopathic hypercalcemia; deletion of elastin gene 7q11.23)
- Clinical presentation—**symptoms depend on severity of obstruction**
  - If severe early in infancy = **critical aortic stenosis** = left ventricular failure and decreased cardiac output
  - **If significant decrease in cardiac output—intensity of murmur at right upper sternal border may be minimal**
  - Mild to moderate—usually asymptomatic with normal growth and development
    - Often discovered with murmur on routine physical examination
    - Rare—older children present with syncope, fatigue, angina, dizziness
  - **With increasing severity—decreased pulses, increased heart size, left ventricular apical thrust**
  - **Early systolic ejection click at apex and left sternal border (does not vary with respiration)**
    - Severe—no click and decreased S1 (decreased left ventricular compliance), decreased S2 (aortic component), and maybe an S4
    - **SEM upper-right second intercostal space; the louder (harsher) and longer the murmur, the greater the degree of obstruction; radiates to neck and left midsternal border; positive thrill in suprasternal notch**
- Diagnosis
  - EKG—**left ventricular hypertrophy** and strain
  - Chest x-ray—**prominent ascending aorta**; may have valve calcification (older children and adults); if severe → increased heart size (left ventricular hypertrophy)
  - **Echocardiogram (gold standard)**
- Treatment
  - Balloon valvuloplasty
  - Surgery on valves
  - Valve replacement

Coarctation of the Aorta

- Narrowing at any point from transverse arch to iliac bifurcation; 90% just below origin of left subclavian artery at origin of ductus arteriosus (juxtaductal coarctation)

Adult versus childhood

- **Discrete juxtaductal coarctation (adult type)**
  - Ascending aortic blood flows normally through narrowed segment to reach descending aorta, but there is left ventricular hypertrophy and hypertension
  - If mild, not recognized until later in childhood
  - Increased blood pressure in vessels proximal to coarctation and decreased blood pressure and pulses below constriction
    - Femoral and other lower pulses weak or absent; bounding in arms and carotids; also **delay in femoral pulse** compared to radial (femoral normally occurs slightly before radial)

Note

Coarctation of the aorta has a high association with Turner syndrome (70% with bicuspid aortic valve).

Note

Coarctation should be suspected in an asymptomatic child with hypertension.

Note

Preductal versus *postductal* is no longer used; it has been found that irrespective of the location, there are only 2 types based on pathology:

- Short, discrete segment of incomplete narrowing which allows for blood flow with left ventricular hypertrophy
- Tubular hypoplasia which does not allow for any hemodynamically significant blood flow; is generally a longer segment of hypoplasia of arch or even distal to ductus

    - Normally, leg systolic pressure is 10–20 mm Hg higher than in arms; in coarctation, leg systolic pressure is decreased (>5%)
    - If pressure is greater in right arm than left arm, suggests coarctation involving left subclavian artery
    - Short systolic murmur along left sternal border at third-to-fourth intercostal space → left scapula and neck
  - Hypertension due not only to mechanical but also to neurohormonal reasons
  - Over time, patient develops an extensive collateral circulation (systolic or continuous murmurs over left and right sides of chest with thrills), **rib notching** (dilated intercostal arteries)
- **Tubular hypoplasia** (**preductal, infantile type**)
  - Severe narrowing starting at one of the head or neck vessels and extending to the ductus
  - Right ventricular blood flows across the PDA to supply the descending aorta so the perfusion of the lower part of the body is dependent upon right ventricular output
  - Seen as differential cyanosis—**upper body is pink**, **lower is cyanotic**; prominent heart failure as ductus closes (if completely atretic = interrupted aortic arch)
  - Presents with lower body hypoperfusion, acidosis, and severe heart failure with ductal closure; large heart, systolic murmur along left sternal border
- Diagnostic tests
  - Chest x-ray—depends on age and effects of hypertension and collaterals
    - Severe (infantile)—increased heart size and pulmonary congestion
    - Adult—findings usually occur after first decade:
      - Increased size of subclavian artery—prominent shadow in left superior mediastinum
      - **Notching of inferior border of ribs** from passive erosion of increased collaterals in late childhood
      - Poststenotic dilatation of ascending aorta
- Diagnosis
  - EKG—left ventricular hypertrophy in older children; in neonates, biventricular hypertrophy
  - Echocardiogram (gold standard)
- Treatment
  - Neonate—PGE_1 infusion to maintain patent, ductus, which establishes adequate lower extremity blood flow; **surgery** after stabilization
  - **Surgery soon after diagnosis of any significant coarctation**
  - Adult—treat heart failure and hypertension, then follow with surgery
- Complications
  - Associated cerebrovascular disease
  - Systemic hypertension
  - Endocarditis
  - Aortic aneurysms

Clinical Recall

A newborn with Noonan syndrome and a cardiac anomaly presents for evaluation. EKG will likely show which of the following?

A. Right ventricular hypertrophy

B. Left ventricular hypertrophy

C. Biventricular hypertrophy

D. Biatrial dilation

E. Left ventricular dilation

Answer: A

RIGHT TO LEFT SHUNTS (CYANOTIC LESIONS)

Cyanotic Lesions Associated with Decreased Pulmonary Blood Flow

Tetralogy of Fallot (TOF)

A 6-month-old infant is prone to episodes of restlessness, cyanosis, and gasping respirations. Symptoms resolve when he is placed in the knee-chest position. Physical examination reveals an underweight infant, with a harsh long systolic ejection murmur and a single second heart sound.

- Components
  - Pulmonary stenosis and infundibular stenosis (obstruction to right ventricular outflow)
  - VSD
  - Overriding aorta (overrides the VSD)
  - Right ventricular hypertrophy
- **Most common cyanotic lesion**
- Pulmonary stenosis plus hypertrophy of subpulmonic muscle (crista supraventricularis) → varying degrees of right ventricular outflow obstruction
  - Blood shunted right-to-left across the VSD with varying degrees of arterial desaturation and cyanosis
  - **If mild, patient may not be visibly cyanotic (pink tetralogy of Fallot)**
    - With growth and further hypertrophy of infundibulum, cyanosis may be seen later in first year of life
  - With severe obstruction, cyanosis in the immediate neonatal period (ductal dependent)
  - If not corrected, older children are blue, have marked clubbing, and have **dyspnea on exertion (child will squat to increase systemic vascular resistance and to decrease right-to-left shunt)**

Note

Common Cyanotic Heart Disease (5 Ts)

Tetralogy of Fallot

Transposition of great vessels

Truncus arteriosus

Total anomalous pulmonary venous return

Tricuspid atresia

  - Paroxysmal hypercyanotic attacks (tet spells)
    - Acute onset of hyperpnea and restlessness → increased cyanosis → gasping → syncope (increased infundibular obstruction with further right-to-left shunting
    - Treatment—place in lateral knee-chest position, give oxygen, subcutaneous morphine, give beta-blockers
- Physical examination—substernal right ventricular impulse, systolic thrill along third-to-fourth intercostal space on left sternal border, loud and harsh systolic ejection murmur (upper sternal border), may be preceded by a click; **either a single S2** or soft pulmonic component
- Diagnosis
  - Chest x-ray—hypertrophied right ventricle causes the apex to be uplifted above the diaphragm → **boot-shaped heart** plus dark lung fields (decreased pulmonary blood flow)
  - EKG—right axis deviation plus right ventricular hypertrophy
  - Echocardiogram (gold standard)
- Pre-correction complications—cerebral thromboses, brain abscess, bacterial endocarditis, heart failure, but not common because of early correction
- Treatment
  - Depends on degree of obstruction
    - PGE_1 infusion—prevent ductal closure; given if cyanotic at birth
    - Augment pulmonary blood flow with **palliative systemic to pulmonary shunt** (modified Blalock-Taussig shunt)
    - Corrective surgery (electively at age 4–12 months)—remove obstructive muscle, valvulotomy, and patching of VSD

Tricuspid atresia

- Pathophysiology—**no outlet from the right atrium to the right ventricle;** entire venous (systemic) return enters the left atrium from a foramen ovale or ASD (**there must be an atrial communication**); left ventricular blood to right ventricle (atretic) via a VSD and is augmented by PDA; **therefore, pulmonary blood flow depends on presence (and size) of VSD**
- Clinical presentation
  - Will present at birth with **severe cyanosis**
  - **Increased left ventricular impulse** (contrast to most others with right ventricular impulse), holosystolic murmurs along left sternal border (most have a VSD; though right ventricle is small, it is still a conduit for pulmonary blood flow)
- Diagnosis
  - Chest x-ray—**pulmonary undercirculation**
  - EKG—**left axis deviation plus left ventricular hypertrophy** (distinguishes from most other congenital heart disease)
  - Echocardiogram (gold standard)
- Treatment
  - **PGE_1 until aortopulmonary shunt can be performed**
  - May need an **atrial balloon septostomy (to make larger ASD)**
  - Later, staged surgical correction

Note

The combination of severe cyanosis in the newborn *plus* a chest x-ray showing decreased pulmonary blood flow *plus* an EKG with left axis deviation and left ventricular hypertrophy is most likely to be **tricuspid atresia.**

Ebstein anomaly

- Development associated with periconceptional maternal **lithium** use in some cases
- **Downward displacement of abnormal tricuspid valve into right ventricle;** the right ventricle gets divided into 2 parts: an atrialized portion, which is thin-walled, and smaller normal ventricular myocardium
- **Right atrium is huge; tricuspid valve regurgitant**
- **Right ventricular output is decreased** because
  - Poorly functioning, small right ventricle
  - Tricuspid regurgitation
  - Variable right ventricular outflow obstruction—abnormal anterior tricuspid valve leaflet. **Therefore, increased right atrial volume shunts blood through foramen ovale or ASD → cyanosis**
- Clinical presentation
  - Severity and presentation depend upon degree of displacement of valve and degree of right ventricular outflow obstruction
    - **May not present until adolescence or adulthood**
    - **If severe in newborn → marked cyanosis, huge heart**
  - **Holosystolic murmur** of tricuspid insufficiency over most of anterior left chest **(most characteristic finding)**
- Diagnosis
  - Chest x-ray—heart size varies from normal to **massive (increased right atrium)**; if severe, **decreased pulmonary blood flow**
  - EKG—tall and broad P waves, right bundle branch block
- Treatment
  - PGE_1
  - Systemic-to-pulmonary shunt
  - Then staged surgery

Note

Patients with Ebstein anomaly may have Wolff-Parkinson-White syndrome (delta wave and short PR interval) and present with episodes of supraventricular tachycardia.

Cyanotic Lesions Associated with Increased Pulmonary Blood Flow

Transposition of the great arteries (TGA)

- Pathophysiology
  - Aorta arises from the right ventricle, and the pulmonary artery arises from the left ventricle; d = dextroposition of the aorta anterior and the right of the pulmonary artery (normal is posterior and to the right of the pulmonary artery)
  - Series circuit changed to **2 parallel circuits; need foramen ovale and PDA** for some mixture of desaturated and oxygenated blood; better mixing in half of patients with a VSD
- Clinical presentation
  - **With intact septum (simple TGA)**—as PDA starts to close, severe cyanosis and tachypnea ensue
  - **S2 usually single and loud** (closure of pulmonic valve obscured by closure of aortic valve)

Note

TGA is the most common cyanotic lesion presenting in the immediate newborn period. It is seen more often in infants of diabetic mothers.

  - If VSD is present, there is a harsh murmur at the lower left sternal border. If large, then holosystolic murmur, significant mixing of blood lessens cyanosis, but presents as heart failure
- Diagnosis
  - Chest x-ray:
    - Mild cardiomegaly, narrow mediastinum, and normal-to-increased pulmonary blood flow
    - **"Egg on a string" appearance**—narrow heart base *plus* absence of main segment of the pulmonary artery
  - EKG—**normal** neonatal right-sided dominance
  - Echocardiogram (gold standard)
- Treatment
  - PGE_1 (keeps PDA patent)
  - Balloon atrial septostomy
  - Arterial switch surgery in first 2 weeks

Note

Truncus arteriosus is one of the major conotruncal lesions associated with the **CATCH-22** syndrome, i.e., DiGeorge. Also seen are transposition of the great arteries and aortic arch abnormalities.

Truncus Arteriosus

- Pathophysiology
  - **Single arterial trunk arises from the heart and supplies all circulations.**
  - **Truncus overlies a ventral septal defect (always present) and receives blood from both ventricles (total mixing).**
  - Both ventricles are at systemic pressure.
- Clinical presentation
  - With dropping pulmonary vascular resistance in first week of life, **pulmonary blood flow is greatly increased and results in heart failure.**
  - Large volume of pulmonary blood flow with total mixing, **so minimal cyanosis**
  - If uncorrected, **Eisenmenger** physiology
  - **Single truncal valve**, which may be incompetent (high-pitched, early diastolic decrescendo at mid-left sternal border)
  - Initially, **SEM with loud thrill, single S2, and minimal cyanosis**
  - With decreasing pulmonary vascular resistance (PVR) → **torrential pulmonary blood flow with heart failure;** runoff from truncus to pulmonary circulation → **wide pulse pressure with bounding pulses and hyperdynamic precordium**
  - Apical mid-diastolic rumble (increased flow across mitral valve)
- Diagnosis
  - Chest x-ray—**heart enlargement with increased pulmonary blood flow**
  - EKG—**biventricular hypertrophy**
  - Echocardiogram (gold standard)
- Treatment
  - **Treat heart failure**
  - Then surgery in first few weeks of life

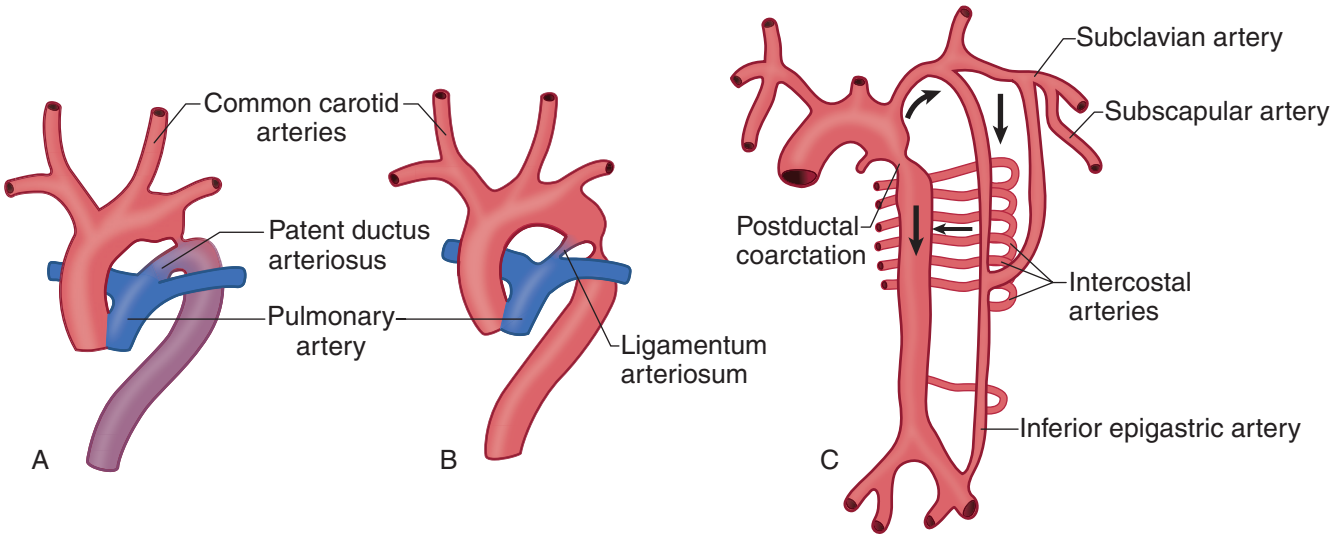
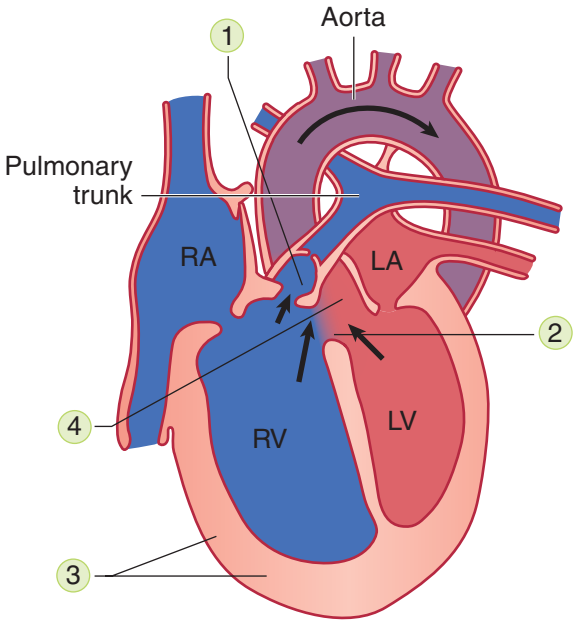


Figure 13-5. Coarctation of the Aorta: (A) Tubular Hypoplasia; (B) Juxtaductal; (C) Collateral Circulation



1. Pulmonary stenosis
2. Ventricular septal defect
3. Hypertrophied right ventricle
4. Overriding aorta

Figure 13-6. Tetralogy of Fallot

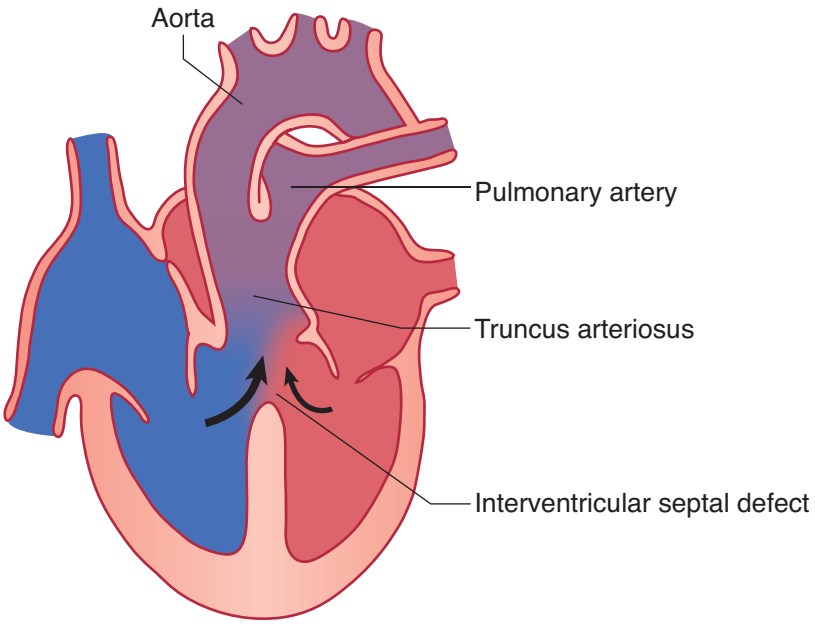


Figure 13-7. Truncus Arteriousus

MIXED LESIONS

Total Anomalous Pulmonary Venous Return (TAPVR)

Note

TAPVR always has an atrial connection.

- Pathophysiology
  - Complete anomalous drainage of the pulmonary veins into the systemic venous circulation; total mixing of **systemic venous and pulmonary venous blood** within the heart produces cyanosis
  - Right atrial blood → right ventricle and pulmonary artery *or* to left atrium via foramen ovale or ASD
  - **Enlarged right atrium, right ventricle, and pulmonary artery; and small left atrium; and left ventricle normal or small**
- **Clinical manifestations** depend on **presence or absence** of obstruction.
  - **Obstruction (of pulmonary veins, usually infracardiac):**
    - **Severe pulmonary venous congestion and pulmonary hypertension with decreasing cardiac output and shock**
    - Cyanosis and severe tachypnea; may not respond to ventilation and PGE_1 → **need emergent diagnosis and surgery for survival**
    - Heart failure early with mild-to-moderate obstruction and a large left-to-right shunt; pulmonary hypertension and mild cyanosis
  - **No obstruction—total mixing with a large left-to-right shunt; mild cyanosis; less likely to be severely symptomatic early**

- Diagnosis
  - Chest x-ray—large supracardiac shadow with an enlarged cardiac shadow forms a **"snowman" appearance**; pulmonary vascularity is increased
  - EKG—**RVH and tall, spiked P waves (RAE)**
  - Echocardiogram (gold standard)
- Treatment: **PGE1; surgical correction**

Hypoplastic Left Heart Syndrome

- Pathophysiology
  - **Atresia of mitral or aortic valves, left ventricle, and ascending aorta (or any combination)**
  - **Right ventricle maintains both pulmonary and systemic circulation.**
  - **Pulmonary venous blood passes through foramen ovale or ASD from left atrium → right atrium and mixes with systemic blood to produce total mixing**
  - Usually, the ventricular septum is intact and all of the right ventricular blood enters the pulmonary artery.
  - **Ductus arteriosus supplies the descending aorta, ascending aorta and coronary arteries from retrograde flow.**
  - Systemic circulation cannot be maintained, and if there is a **moderate-to-large ASD → pulmonary overcirculation**
- Clinical presentation
  - **Cyanosis may not be evident with ductus open,** but then **gray-blue** skin color (combination of hypoperfusion and cyanosis as ductus closes)
  - **Signs of heart failure, weak or absent pulses, and shock**
  - Enlarged heart with **right parasternal lift;** nondescript systolic murmur
- Diagnosis: chest x-ray shows **heart enlargement with increased pulmonary blood flow**; EKG shows **right ventricular hypertrophy** and **right atrial enlargement with decreased left-sided forces**; echocardiogram (gold standard)

Treatment: **consider doing nothing** if malformations or genotype not compatible with life; best treatment is **3-stage Norwood procedure** (better result than cardiac transplantation)

- Other: many patients have a significant **abnormality of central nervous system (CNS)** and/or kidneys: **need careful genetic, neurologic examination and screening tests on any child being considered for surgery**

Clinical Recall

Which of the following cardiac anomalies is correctly matched to its classic chest x-ray findings?

A. Hypoplastic left heart syndrome: normal cardiac silhouette with decreased pulmonary vascularity

B. TAPVR: snowman sign with increased pulmonary vascularity

C. Truncus arteriosus: egg on a string sign

D. TGA: massively enlarged right atrium

E. Tricuspid atresia: boot-shaped heart

Answer: B

REGURGITANT LESIONS

Mitral Valve Prolapse

Note

Mitral valve prolapse is a common finding in those with Marfan and Ehlers-Danlos syndrome.

- Abnormal cusps—billowing of one or both leaflets into left atrium from mid to late systole (congenital defect: entire MV complex undergoes myxomatous degeneration, which leads to redundant tissue of the chordae tendineae)
- Usually not recognizable until adolescence or adulthood; girls > boys
  - May present with chest pain or palpitations
  - Arrhythmias, especially uni- or multifocal premature ventricular contractions
- **Mid-systolic click followed by mid- to late-blowing decrescendo systolic murmur**
- Diagnosis: EKG usually normal; chest x-ray normal; echocardiogram (gold standard)
- No therapy, not progressive; adults (more in men) at risk for cardiovascular complications if have thickened leaflets

OTHER CARDIAC PATHOLOGY

Infective Endocarditis

A 6-year-old boy has had high intermittent fevers for 3 weeks, accompanied by chills. He has a past history of bicuspid aortic valves and recently had dental work.

Note

Staphylococcal endocarditis is more common in those without underlying heart disease. *Streptococcus viridans* is more common in patients *with* underlying heart disease or after dental procedures.

- Etiology/epidemiology
  - Most are *Streptococcus viridans* (alpha hemolytic) and *Staphylococcus aureus*
  - Organism associations
    - *S. viridans*—after dental procedures
    - Group D streptococci—large bowel or genitourinary manipulation
    - *Pseudomonas aeruginosa* and *Serratia marcescens*—intravenous drug users
    - Fungi—after open heart surgery
    - Coagulase-negative *Staphylococcus*—indwelling intravenous catheters

  - Highest risk with prosthetic valve and uncorrected cyanotic heart lesions
  - Most cases occur after **surgical or dental procedures** (high risk with poor dental hygiene) are performed.
- Clinical presentation
  - **Prolonged intermittent fever, weight loss,** fatigue, myalgia, arthralgia, headache, nausea, vomiting
  - **New or changing heart murmur**
  - Splenomegaly, petechiae, embolic stroke, CNS abscess, CNS hemorrhage, mycotic aneurysm (all more with *Staphylococcus*)
  - Skin findings (rare): late findings (uncommon in treated patients); represent vasculitis from circulating Ag-Ab complexes; if present, are highly suggestive
    - **Osler nodes**—tender, pea-sized, intradermal nodules on pads of fingers and toes
    - **Janeway lesions**—painless, small erythematous or hemorrhagic lesions on palms and soles
    - **Splinter hemorrhage**—linear lesions beneath nail beds
    - **Roth spots**—retinal exudates
- Diagnosis
  - Two separate positive blood cultures plus echocardiographic evidence of intracardiac or valve lesion; prosthetic regurgitant flow; abscess; partial dehiscence of prosthetic valve or new valvular regurgitant flow

Table 13-3. Duke Criteria

Major Criteria	Minor Criteria
• **Positive blood culture** (2 separate for usual pathogens; at least 2 for less common) • Evidence on **echocardiogram** (intracardiac or valve lesion, prosthetic regurgitant flow, abscess, partial dehiscence of prosthetic valve, new valvular regurgitant flow)	• Predisposing conditions • Fever • Emboli or vascular signs • Immune complex disease (glomerulonephritis, arthritis, positive rheumatoid factor, Osler node, Roth spots [retinal hemorrhages with white centers]) • Single positive blood culture • Echocardiographic signs not meeting criteria

- Complications
  - **Most common—heart failure from aortic or mitral lesions**
  - Others—systemic or pulmonary emboli, myocardial abscess, myocarditis, valve obstruction, heart block, meningitis, osteomyelitis, arthritis, renal abscess, immune complex–mediated glomerulonephritis
- Treatment
  - Organism specific for 4–6 weeks (*S. viridans*, Enterococci, *S. aureus,* MRSA, *S. epidermidis*, HACEK)
  - Heart failure—digitalis, diuretic, salt restriction
  - Surgery with severe involvement or lack of improvement

Note

Clinical diagnosis of **infective endocarditis** is made with one of the following:

- 2 major
- 1 major + 3 minor
- 5 minor

Note

HACEK

- *Haemophilus* spp.
- *Actinobacillus actinomycetemcomitans*
- *Cardiobacterium hominis*
- *Eikenella corrodens*
- *Kingella kingae*

These are slow-growing gram-negative organisms that are part of normal flora.

- Prophylaxis (AHA, 2007) for:
  - Artificial valves
    - Previous history of infective endocarditis
    - Unrepaired or incompletely repaired cyanotic disease, including those with palliative shunts and conduits
    - A completely repaired defect with prosthetic material or device for first 6 months
    - Any residual defect at site of any repair
    - Cardiac transplant which develops a problem in a valve
    - Given ONLY for dental procedures with manipulation of gingival tissue or periapical area or perforation of oral mucosa; incision or biopsy of respiratory tract mucosa and surgery on infected skin or musculoskeletal structures
    - Drug of choice is amoxicillin

Acute Rheumatic Fever

A 6-year-old girl complains of severe joint pain in her elbows and wrists. She has had fever for the past 4 days. Past history reveals a sore throat 1 month ago. Physical examination is remarkable for swollen, painful joints and a heart murmur. Laboratory tests show an elevated erythrocyte sedimentation rate and high antistreptolysin (ASO) titers.

- Etiology/epidemiology
  - Related to group A *Streptococcus* infection within several weeks
  - Antibiotics that eliminate *Streptococcus* from pharynx prevent initial episode of acute rheumatic fever
  - Remains **most common form of acquired heart disease worldwide** (but Kawasaki in United States and Japan)
  - Initial attacks and recurrences with peak incidence *Streptococcus* pharyngitis: age 5–15
  - Immune-mediated—antigens shared between certain strep components and mammalian tissues (heart, brain, joint)
- Clinical presentation and diagnosis—Jones criteria. Absolute requirement: evidence of recent *Streptococcus* infection (microbiological or serology); then 2 major or 1 major and 2 minor criteria

Note

If arthritis is present, arthralgia cannot be used as a minor criterion.

The presence of Sydenham chorea alone is sufficient for diagnosis.

Table 13-4. Jones Criteria

Major Criteria	Minor Criteria
Carditis	Fever
Polyarthritis (migratory)	Arthralgia
Erythema marginatum	Elevated acute phase reactants (ESR, CRP)
Chorea	Prolonged PR interval on EKG
Subcutaneous nodules	*Plus* evidence of preceding streptococcal infection

- Treatment
  - Bed rest and monitor closely
  - **Oral penicillin** or erythromycin (if allergic) for 10 days will eradicate group A strep; then need long-term prophylaxis
  - Anti-inflammatory
    - **Hold if arthritis is only typical manifestation (may interfere with characteristic migratory progression)**
    - Aspirin in patients with arthritis/carditis *without* CHF
    - If carditis with CHF, **prednisone** for 2–3 weeks, then taper; start aspirin for 6 weeks
  - Digoxin, salt restriction, diuretics as needed
  - **If chorea is only isolated finding, do not need aspirin; drug of choice is phenobarbital** (then haloperidol or chlorpromazine)
- Complications
  - Most have no residual heart disease.
  - **Valvular disease most important complication (mitral, aortic, tricuspid)**
- Prevention
  - **Continuous antibiotic prophylaxis**
    - If carditis—continue into adulthood, perhaps for life; without carditis—lower risk; can discontinue after patient is in their twenties and at least 5 years since last episode
    - Treatment of choice—**single intramuscular benzathine penicillin G** every 4 weeks
    - If compliant—penicillin V PO BID or sulfadiazine PO QD; if allergic to both: erythromycin PO BID

Hypertrophic Obstructive Cardiomyopathy (HOCM)

- Pathophysiology
  - **Obstructive left-sided congenital heart disease**
- Decreased compliance, so increased resistance and **decreased left ventricular filling,** mitral insufficiency
- Clinical presentation—weakness, fatigue, dyspnea on exertion, **palpitations, angina, dizziness, syncope; risk of sudden death**
- Cardiovascular examination—**left ventricular lift, no systolic ejection click (differentiates from aortic stenosis),** SEM at left sternal edge and apex (increased after exercise, during Valsalva, and standing)
- Diagnosis
  - EKG—left ventricular hypertrophy ± ST depression and T-wave inversion; may have intracardiac conduction defect
  - Chest x-ray—mild cardiomegaly (prominent LV)
  - Echocardiogram—left ventricular hypertrophy, mostly septal; Doppler—left ventricular outflow gradient usually mid-to-late systole (maximal muscular outflow obstruction)
- Treatment
  - **No competitive sports or strenuous exercise (sudden death)**
  - **Digoxin and aggressive diuresis are contraindicated** (and infusions of other inotropes)
  - **Beta blockers (propranolol) and calcium channel blockers (verapamil)**

Note

Suspect hypertrophic cardiopathy in an athlete with sudden death.

Clinical Recall

A 16-year-old girl seen in clinic last month for strep throat returns with a few weeks of knee pain that is resolving and 2 days of worsening elbow pain despite no recent trauma. In addition, she has noticed several small ring-like rashes on her arms and abdomen that come and go. What additional finding is needed to diagnose acute rheumatic fever?

A. Cardiac inflammation

B. EKG showing PR interval prolongation

C. Chorea

D. No additional findings are needed

E. Elevated ESR and CRP

Answer: D

HYPERTENSION

A 5-year-old girl is noted to have blood pressure >95th percentile on routine physical examination. The rest of the examination is unremarkable. Her blood pressure remains elevated on repeat measurement over the next few weeks. Past history is remarkable for a treated urinary tract infection 1 year ago. Complete blood cell count is normal; urinalysis is normal. Blood urea nitrogen is 24 mg/dL and creatinine is 1.8 mg/dL.

Note

When a child presents with hypertension, think of renal causes.

- Routine blood pressure check beginning at 3 years of age
  - If increased blood pressure, check all 4 extremities (coarctation)
  - Normal—blood pressure in legs should be 10–20 mm Hg higher than in arms
  - If obese, on medications which increase BP, diabetes, or chronic kidney disease, check blood pressure
- Blood pressure increases with age—need standard nomograms
  - If mild hypertension, repeat twice over next 6 weeks
  - If consistently >95% for age, need further evaluation
  - ≥95th percentile at 3 different visits
- Etiology—essential (primary) or secondary
  - Secondary—**most common in infants and younger children**
    - Newborn—umbilical artery catheters → renal artery thrombosis
    - Early childhood—renal disease, coarctation, endocrine, medications
    - Adolescent—essential hypertension

  - **Renal and renovascular hypertension—majority of causes may be due to urinary tract infection** (secondary to an obstructive lesion), acute glomerulonephritis, Henoch-Schönlein purpura with nephritis, hemolytic uremic syndrome, acute tubular necrosis, renal trauma, leukemic infiltrates, mass lesions, renal artery stenosis
  - Essential hypertension—more common in adults and adolescents
    - Positive family history
    - Multifactorial—obesity, genetic, and physiologic changes
- Diagnosis
  - CBC, blood chemistries, UA, EKG, echo, renal ultrasound, angiogram (less common)
- Treatment
  - If obese—weight control, aerobic exercise, no-added-salt diet, monitor blood pressure
  - Pharmacologic treatment (secondary hypertension and selective primary)—similar use of drugs as in adults
  - No real workup age ≥6 years and family history, obese, with normal history and physical
  - DASH diet (Dietary Approaches to Stop Hypertension)

Gastrointestinal Disease 14

Learning Objective

- ❑ Diagnose and describe treatments for children who present with gastroenteritis, vomiting, hematochezia, or constipation

GASTROENTERITIS

Acute Diarrhea

A 13-month-old child has had a 3-day history of green watery stools. She has also been vomiting for 1 day. Physical examination reveals a febrile, irritable baby with dry mucous membranes and sunken eyes.

- Etiology

Table 14-1. Causes of Diarrhea (Acute and Chronic)

	Infant	Child	Adolescent
Acute	• Gastroenteritis • Systemic infection • Antibiotic	• Gastroenteritis/ Food poisoning • Systemic infection	• Gastroenteritis/ food poisoning • Systemic infection
Chronic	• Postinfectious lactase deficiency • Milk/soy intolerance • Chronic diarrhea of infancy • Celiac disease • Cystic fibrosis	• Postinfectious lactase deficiency • Irritable bowel syndrome • Celiac disease • Lactose intolerance • *Giardiasis* • Inflammatory bowel disease	• Irritable bowel syndrome • Inflammatory bowel disease • Lactose intolerance • *Giardiasis* • Laxative abuse

Note

Common Causes of Bloody Diarrhea

- *Campylobacter*
- Amoeba (*E. histolytica*)
- *Shigella*
- *E. coli*
- *Salmonella*

- Common organisms

Table 14-2. Common Causes of Acute Diarrhea

Bacterial (Inflammatory)	Viral	Parasitic
Campylobacter	**Norovirus**	***Giardia lamblia* (most common)**
Enteroinvasive *E. coli*	Rotavirus	*E. histolytica*
Salmonella	Enteric adenovirus	*Strongyloides*
Shigella	Astrovirus	*Balantidium coli*
Yersinia	Calicivirus	*Cryptosporidium parvum*
Clostridium difficile		*Trichuris trichiura*
E. coli 0157:H7		

- Major transmission is **fecal/oral** or by **ingestion of contaminated food or water**
- Clinical presentation
  - Diarrhea, vomiting, abdominal cramps, nausea, fever (suggests inflammation and dehydration)
  - Can present from an **extraintestinal infection**, e.g., urinary tract infection, pneumonia, hepatitis
- Management
  - **Assess hydration and provide fluid and electrolyte replacement**
  - Prevent spread
  - In some cases, determine etiology and provide specific therapy (some are not treated)
  - Think about **daycare** attendance, recent **travel,** use of **antibiotics,** exposures, intake of **seafood, unwashed vegetables, unpasteurized milk, contaminated water, uncooked meats to isolate differential diagnosis of organisms**
- Labs: **stool examination** (cost-effective, noninvasive)
  - Mucus, blood, leukocytes → colitis (invasive or cytotoxic organism)
  - Stool cultures—with blood, leukocytes, suspected hemolytic uremic syndrome, immunosuppressed, in outbreaks
  - *Clostridium difficile* toxin—if recent history of antibiotics
  - Ova and parasites
  - Enzyme immunoassays for viruses or PCR (rarely need to be diagnosed)

Note

Antidiarrheal compounds should never be used in children.

Chronic Diarrhea

Table 14-3. Organism-Specific Associations and Therapy

Organism	Association	Therapy
Rotavirus	Watery diarrhea, vomiting, ± fever	Supportive
Enteropathogenic *E. coli*	Nurseries, daycare	Mostly supportive care
Enterotoxigenic *E. coli*	Traveler's diarrhea	Supportive care with trimethoprim sulfamethoxazole in severe cases
Enterohemorrhagic *E. coli*	Hemorrhagic colitis, HUS	**No antibiotic therapy** due to ↑ risk of HUS; supportive care only
Salmonella	Infected animals and contaminated eggs, milk, poultry	Antibiotics indicated *only* for patients who are ≤3 months of age, toxic, has disseminated disease, or *S. typhi*
Shigella	Person-to-person spread, contaminated food	Trimethoprim/sulfamethoxazole
Campylobacter	Person-to-person spread, contaminated food	Self-limiting; erythromycin for severe disease
Yersinia enterocolitica	Pets, contaminated food	No antibiotics except for infants ≤3 months of age or culture-proven septicemia
Clostridium difficile	History of antibiotic use	Metronidazole or vancomycin
Staphylococcus aureus	Food poisoning (onset within 12 h of ingestion)	Supportive care
Entamoeba histolytica	Acute bloody diarrhea	Metronidazole
Giardia	Chronic or intermittent watery diarrhea, abdominal distension, nausea, weight loss, intermittent crampy abdominal pain Contaminated food or water or from infected person	Tinidazole is the FDA-recommended therapy (single dose; has replaced furazolidone)
Cryptosporidium	Mild diarrhea in immunocompromised infants; severe diarrhea in AIDS patients	Best treatment is raising CD4 count to normal level + supportive care

Definition of abbreviations: HUS, hemolytic uremic syndrome

Chronic Diarrhea and Malabsorption

- Patterns
  - From birth
  - After introduction of a new food
- Clinical presentation
  - Chronic nonspecific diarrhea of infancy:
    - **Weight, height, and nutritional status is normal, and no fat in stool**
    - Excessive intake of fruit juice, carbonated fluids, low fat intake usually present in history
  - Diarrhea with carbohydrates—CHO malabsorption
  - Weight loss and stool with high fat—think malabsorption
  - Other signs and symptoms suggest other specific diagnosis; see side note
- Workup of chronic diarrhea (simple, noninvasive testing to be done first)
  - History and physical, nutritional assessment; **stool** for pH, reducing substances, fat, blood, leukocytes, culture, *C. difficile* toxin, ova, and parasites
  - Blood studies—complete blood count and differential, ESR, electrolytes, glucose, BUN, and creatinine
  - **Sweat test, 72-hour fecal fat,** breath hydrogen tests
- Initial evaluation
  - Fat:
    - **Most useful screening test is stool for fat (Sudan red stain)**
    - **Confirm with 72-hour stool for fecal fat (gold standard for steatorrhea)**
    - **Steatorrhea is most prominent with pancreatic insufficiency; all require a sweat chloride**
    - Serum trypsinogen is also a good screen (reflects residual pancreatic function; increased level at birth in CF)
  - CHO malabsorption—screen with **reducing substances in stool (Clinitest)**
    - **Breath hydrogen test**—after a known CHO load, the collected breath hydrogen is analyzed and malabsorption of the specific CHO is identified
  - Protein loss—cannot be evaluated directly (large proportion of bacterial protein and dietary protein almost completely absorbed before terminal ileum; amino acids and peptides are reabsorbed)
    - Screen—**spot stool α_1-antitrypsin level**
- More common differential diagnosis of malabsorption
  - **Giardiasis—only common primary infection causing chronic malabsorption;** stool test for *Giardia* antigen duodenal aspirate and biopsy (best test)
  - HIV or congenital T- or B-cell defects
  - Small-bowel disease—**gluten enteropathy**, abetalipoproteinemia, lymphangiectasia
  - Pancreatic insufficiency—fat malabsorption (**cystic fibrosis is most common congenital disorder associated with malabsorption**)
  - Most common anomaly causing incomplete bowel obstruction with malabsorption is **malrotation**
  - **Short bowel**—congenital or postnatal loss of >50% of small bowel with or without a portion of the large intestine (presence of ileocecal valve is better)

Note

Schwachman-Diamond Syndrome
- Pancreatic insufficiency
- Neutropenia
- Malabsorption

Intestinal lymphangiectasia
- Lymph fluid leaks into bowel lumen
- Steatorrhea
- Protein-losing enteropathy

Disaccharidase Deficiency
- Osmotic diarrhea
- Acidic stools

Abetalipoproteinemia
- Severe fat malabsorption from birth
- Acanthocytes
- Very low to absent plasma cholesterol, triglycerides, etc.

- **Celiac disease**—associated with exposure to **gluten** (mostly rye, wheat, barley)
  - Patients—mostly 6 months to 2 years; **permanent intolerance**; genetic predisposition (HLA DQ2)
  - Clinical presentation—diarrhea, failure to thrive, growth restriction, vomiting, anorexia, ataxia
  - Evaluation—best initial test is blood test for anti-tissue-transglutaminase (IgA) + serum IgA (false if IgA is also deficient); definitive test is small bowel biopsy
  - Treatment—**lifelong, strict gluten-free diet**

Clinical Recall

A 14-year-old boy presents with watery diarrhea and nausea after a hiking trip during which he swam in a small freshwater lake. What is the treatment of choice?

A. Supportive care with rest and fluids

B. Trimethoprim/sulfamethoxazole

C. Metronidazole

D. Neomycin

E. Cefuroxime

Answer: C

VOMITING

Esophageal Atresia (EA) and Tracheoesophageal Fistula (TEF)

- Three basic types:
  - Isolated EA
  - Isolated (H-type) TEF
  - EA and distal TEF
- Most common anatomy is **upper esophagus ends in blind pouch and TEF connected to distal esophagus**
- **H-type—presents chronically** and diagnosed later in life with chronic respiratory problems
- Half with associated anomalies—**VACTERL** association
- Clinical presentation in neonate (EA or EA + TEF)
  - **At birth—history of polyhydramnios; frothing, bubbling through nose and mouth; suctioning copious amount of fluid; respiratory distress, cyanosis from airway obstruction, amniotic fluid aspiration**
  - **With feedings → immediate regurgitation and aspiration**
- Clinical presentation with just TEF—feeding problems and recurrent aspiration

Note

VACTERL Association

Nonrandom association of birth defects:

Vertebral anomalies

Anal atresia

Cardiac defect

TracheoEsophageal fistula

Renal anomalies

Limb abnormalities

- Diagnosis
  - **Inability to pass nasogastric/orogastric tube**
  - Esophageal atresia: x-ray shows coiled nasogastric tube in blind pouch with no distal gas (gasless abdomen)
  - **Isolated** TEF: **esophagram with contrast media** (or bronchoscopy or endoscopy with methylene blue)
  - Esophageal atresia and distal fistula: coiled nasogastric tube in blind pouch the large amount of air in stomach and intestines
- Treatment—surgical ligation of TEF and resection with end-to-end anastomosis of esophageal atresia

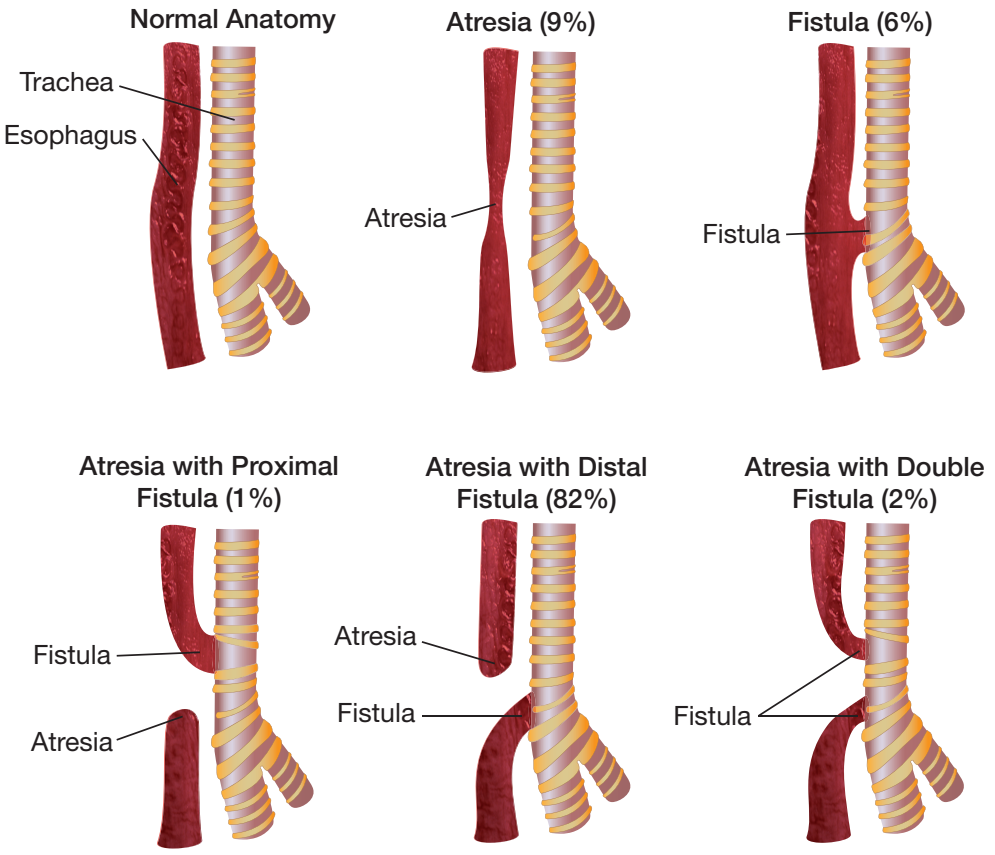


Figure 14-1. Tracheoesophageal Fistula (TEF) Types

Gastroesophageal Reflux Disease (GERD)

A 4-month-old is admitted with episodes of apnea occurring 20–30 min after feeds. The mother states the baby has been spitting up since birth. She is at the 5th percentile for weight.

Almost all infants have some degree of reflux (mild to moderate) from birth due to slow development of lower gastroesophageal sphincter tone development. Improvement is seen over the first months and almost always resolves by age 12-24 months. Older children are clinically like adults; only about 50% spontaneously resolve.

Most cases present as postprandial regurgitation, significantly fewer as esophagitis or recurrent aspiration. Clinical findings usually raise suspicion of this diagnosis; barium esophagram determines if recurrent aspiration is due to GERD or TE fistula. The best test (which is also quantitative) is an in-hospital overnight pH study. Endoscopy is used for presumptive reflux esophagitis.

Treatment is mostly conservative, with the addition of H2 blockers or PPI for severe cases and esophagitis. Fundoplication is used for refractive disease.

Pyloric Stenosis

A 4-week-old boy has nonbilious projectile vomiting. Physical examination is remarkable for a small mass palpated in the abdomen.

Note

Pyloric stenosis is high yield for the exam.

- Epidemiology—more common in whites of Northern European ancestry, **firstborn males**
- Clinical presentation
  - **Nonbilious, projectile vomiting**
  - **Still hungry and desire to feed more**
  - Usually age **≥3 weeks (1 week to 5 months)**
  - Mild-to-moderate dehydration, **hypochloremic, hypokalemic metabolic alkalosis**
  - Palpation of a firm, movable, 2-cm, **olive-shaped,** hard mass in midepigastrium; left to right peristaltic wave
- Diagnosis—best test is **ultrasound** (a target-like appearance in cross-section)
- Treatment
  - Rehydrate, correct electrolytes (NaCl, KCl)
  - **Pyloromyotomy**

Duodenal Atresia

A newborn presents with bilious vomiting with every feed. Abdominal film reveals a double bubble.

- Epidemiology
  - Half are born premature
  - **Down syndrome**
  - With other anomalies—malrotation, esophageal atresia, congenital heart defects, anorectal malformation, renal anomalies
- Clinical presentation
  - **Bilious vomiting *without* abdominal distention on first day of life** (obstruction just distal to ampulla)
  - **Polyhydramnios** prenatally
  - Many with **jaundice** (increased enterohepatic circulation)
- Diagnosis
  - X-ray shows classic **double bubble with *no* distal bowel gas.**
  - X-ray spine for anomalies; ultrasound for other anomalies
- Treatment
  - **Nasogastric decompression**
  - Intravenous fluids
  - **Surgery**—duodenoduodenostomy

Clinical Recall

A newborn is diagnosed with a tracheoesophageal fistula. What additional anomaly is she most likely to have?

A. Pulmonary stenosis

B. Sternal dysplasia

C. Oral atresia

D. Renal agenesis

E. Ectopia lentis

Answer: D

Note

Jejunal or Ileal Atresia

- Often presents on day 1 of life
- Bile-stained emesis with abdominal distention (unlike duodenal atresia, which has no abdominal distention)

Plain x-ray shows air-fluid level

- Contrast study of upper/lower intestine highlight level of obstruction
- U/S may differentiate intestinal atresia from meconium ileus from malrotation

Table 14-4. Congenital Bowel Obstruction

Lesion	Etiology	DDX	Clinical Background/ Presentation	Diagnosis	Management Algorithm/Definitive Treatment
Duodenal Atresia	Failed recanalization of bowel lumen 4th–7th week gestation	• Duodenal stenosis • Annular pancreas • Duplication cysts • Ladd bands from malrotation	• Polyhydramnios • 50% premature • Other organ system anomalies • Half with chromosomal anomalies, especially trisomy 21 **Presentation** • First day • Bilious vomiting w/o abdominal distention • Jaundice	• **Prenatal sonogram** • **Postnatal plain x-ray:** double-bubble with NO distal bowel gas • **CXR, spine films** • **Echocardiogram** • **Renal ultrasound** for other most common anomalies	• NG/OG decompression • NPO + IV fluids + electrolyte balance • Broad-spectrum antibiotics **Definitive Treatment:** **Surgery when stable—** duodenoduodenostomy
Jejunal and Ileal Atresias	Intrauterine vascular accident → segmental infarction and resorption of fetal intestine	• Meconium ileus/plug • Malrotation ± volvulus • Hirschsprung disease	• Possible role with antenatal cigarette and/or cocaine use • Very little familial inheritance (aut. rec.) • Little extraintestinal anomalies **Presentation** • Polyhydramnios • Abdominal distention at birth or with first feeds + vomiting, may be bilious • Few with delayed or no passage of meconium • Jaundice	• Less likely to be detected in utero • **Plain x-ray:** multiple air-fluid levels proximal to obstruction in upright or lateral decubitus • **Ultrasound:** differentiate with meconium ileus and identify malrotation • **Contrast studies** to localize	• NG/OG • IV fluid and electrolyte balance prior to surgery • Antibiotics **Definitive Treatment:** **Surgery—**resect dilated proximal bowel, then end-to-end anastomosis

(Continued)

Table 14-4. Congenital Bowel Obstruction (*Cont'd*)

Lesion	Etiology	DDX	Clinical Background/ Presentation	Diagnosis	Management Algorithm/ Definitive Treatment
Meconium Ileus	Abnormal viscous secretions → distal 20-30 cm of ileum collapsed and proximal bowel dilated and filled with thick meconium impacted in ileum	• Meconium plug • Atresias • Hirschsprung disease • Malrotation ± volvulus	• 80-90% will be diagnosed with CF • May perforate in utero → meconium peritonitis (calcifications) **Presentation:** • Vomiting becomes persistent with prominent abdominal distention • No passage of meconium • May present as bowel perforation and peritonitis • Palpation of "doughy" or cordlike masses	• **Plain films:** dilated loops of bowel proximal to obstruction that vary with width and not evenly filled with gas • Presence of bubbly or granular appearance in RLQ (meconium with gas bubbles) • No air-fluid levels as secretions are too viscid to layer • **Ultrasound** to verify if questionable • **Water-soluble enema** (Gastrografin or Hypaque) will localize • **Test for CF**	• NPO • NG/OG decompression • IV fluid and electrolyte balance • Antibiotics **Definitive Treatment:** **First:** hypertonic water-soluble contrast enema to attempt wash-out **If fails**—laparotomy
Meconium Plugs	Decreased water content for many possible reasons leads to lower colonic or anorectal meconium plug	• Meconium ileus • Hirschsprung disease	• Majority not associated with CF, unless in small bowel • Infants with polycythemia, dehydration and small left colon as may be seen with IODM • Maternal opiate use or treatment with MgSO4 **Presentation:** Failure of meconium passage and abdominal distention	• **Plain films**: low obstruction with proximal bowel dilatation and multiple air-fluid levels	• NG/OG + NPO • IV fluid and electrolyte balance • Antibiotics **Definitive Treatment:** • Evacuation with glycerin suppository if very low or saline enema or hypertonic water-soluble contrast if higher • Observe for possible Hirschsprung disease • Consider sweat test if contrast shows small bowel plug.

Table 14-4. Congenital Bowel Obstruction (*Cont'd*)

Lesion	Etiology	DDX	Clinical Background/ Presentation	Diagnosis	Management Algorithm/ Definitive Treatment
Malrotation	• As developing bowel rotates in and out of abdominal cavity (weeks 5-12), superior mesenteric artery acts as the axis • With nonrotation, 1st and 2nd part of duodenum are in normal position, but because of inadequate mesenteric attachment to posterior wall, rest of small bowel occupies RLQ and colon the left • Failure of cecum to move to the RLQ → failure to form broad-based adhesions to posterior wall → superior mesenteric artery is tethered by a narrow stalk (causes volvulus) and Ladd bands can extend from cecum to RUQ and obstruct at duodenum.	• Intestinal atresias • Meconium ileus • Hirschsprung disease	• Other anomalies of abdominal wall – Diaphragmatic hernia – Gastroschisis – Omphalocele – Heterotaxy syndrome (CHD, malrotation, asplenia/ polysplenia) **Presentation:** • 1st year of life with >50% in first month with symptoms due to intermittent volvulus and/or Ladd band obstruction -acute and chronic obstruction (recurrent pain and vomiting) • Can present in first week with bilious emesis and acute obstruction • May have, malabsorption due to bacterial overgrowth • Any age with acute obstruction due to volvulus	• **Plain film:** may show double-bubble with evidence of small amount of distal gas (prior to the volvulus) or a gasless abdomen • **Ultrasound:** inversion of superior mesenteric artery and vein • **Upper GI:** malposition of ligament of Treitz and small bowel obstruction with corkscrew appearance or duodenal obstruction with "bird's beak" appearance	• **If volvulus:** emergency surgery after IV and fluids • Otherwise NPO, NG/ OG • Correct fluid and electrolyte imbalance. **Definitive Treatment:** • **Surgery:** any patient of any age with any significant rotational abnormality • **Volvulus:** acute surgical emergency

(Continued)

Table 14-4. Congenital Bowel Obstruction (*Cont'd*)

Lesion	Etiology	DDX	Clinical Background/ Presentation	Diagnosis	Management Algorithm/ Definitive Treatment
Hirschsprung Disease	• Developmental disorder of the enteric nervous system such that there are absence of ganglion cells in the submucosal and myenteric plexus • Arrest of neuroblast migration from proximal to distal bowel → inadequate relaxation and hypertonicity	• Long segment disease vs. intestinal atresia • Meconium plug • Meconium ileus	• Most common cause of intestinal obstruction in neonate • Usual short segment is male preponderance but equalizes with long segment disease • Increased familial incidence with long segment but must (short segment) are sporadic • May be associated with cardiovascular and urological defects and with Down syndrome • 80% are short (rectosigmoid) • 10-15% long (more than that) • 5% total bowel aganglionosis **Presentation:** • Most diagnosed in neonates • Suspect with any delayed meconium passage in full-term infant (99% within first 48 hours) or no passage with progressive abdominal distension and vomiting • Later with chronic constipation and empty rectum on digital exam with subsequent explosive release of small stool and gas • Main concern is meconium enterocolitis	• **Plain film:** distended loops of bowel • **Contrast enema** may not show classic line of demarcation from small aganglionic bowel to proximal dilatation (better >1 month of age) but 24 hr films usually show retained contrast and suggest the diagnosis • **Barium enema** also useful prior to surgery to define extent of aganglionic segment • **Gold standard confirmation is the suction rectal biopsy**	• NG/OG • NPO • Fluid and electrolyte management • Evaluate for other defects **Definitive Treatment:** Laparoscopic single-stage endorectal pull-through is procedure of choice.

Malrotation and Volvulus

- Etiology
  - **Incomplete rotation of intestine during fetal development**
  - Superior mesenteric artery acts as axis for rotation
  - **Ladd bands may extend from cecum to right upper quadrant (RUQ) to produce duodenal obstruction**
- Clinical presentation
  - Most present in first year of life with acute or chronic incomplete obstruction
  - **Bilious emesis, recurrent abdominal pain with vomiting**
  - **An acute small-bowel obstruction in a patient without previous bowel surgery is suspicious for volvulus (acute surgical abdomen)**
- Diagnosis
  - Plain film is nonspecific—may show double bubble if there is duodenal obstruction
  - Barium enema shows malposition of cecum (mobile cecum is not situated in the right lower quadrant); upper gastrointestinal will show malposition of ligament of Treitz
  - **Ultrasound will show inversion of superior mesenteric artery and vein (superior mesenteric vein to the left of the artery is suggestive) and duodenal obstruction with thickened bowel loops to the right of the spine; advantage is no need for contrast; start with this study**
- Treatment—surgery

Clinical Recall

A 3-week old infant girl with bilious emesis has an abdominal x-ray with a double-bubble sign and a small amount of air in the distal small bowel loops. What imaging test should be ordered to confirm the diagnosis, and what are the expected findings?

A. None: go straight to surgery

B. Water-soluble enema: no passage through the ileocecal valve

C. Barium enema: small rectum and dilated sigmoid colon

D. Ultrasound: increased thickness of the pylorus

E. Upper GI series: corkscrew appearance of the duodenum

Answer: E

Note

A delay in treating volvulus can result in short bowel syndrome.

Note

Meckel diverticulum: "Disease of 2s"

- 2 years of age
- 2% of population
- 2 types of tissue
- 2 inches in size
- 2 ft from ileocecal valve
- Male:female 2:1

HEMATOCHEZIA

Meckel Diverticulum

A 2-year-old boy presents with a 1-week history of painless rectal bleeding. Physical examination is unremarkable. The abdomen is soft and nontender. Rectal examination is unremarkable.

- Etiology
  - Remnant of embryonic yolk sac (omphalomesenteric or vitelline duct), **lining similar to stomach**
  - **Most frequent congenital gastrointestinal anomaly**
- Clinical presentation
  - Acid-secreting mucosa causes **intermittent painless rectal bleeding**
  - May get anemia, but blood loss is self-limited
  - May have partial or complete bowel obstruction (lead point for an intussusception) or develop diverticulitis and look like acute appendicitis (much less common presentation)
- Diagnosis—**Meckel radionuclide scan** (Tc-99m pertechnetate)
- Treatment—**surgical excision**

Intussusception

A 15-month-old child is seen for cramping, colicky abdominal pain of 12 h duration. He has had 2 episodes of vomiting and a fever. Physical examination is remarkable for a lethargic child; abdomen is tender to palpation. Leukocytosis is present. During examination, the patient passes a bloody stool with mucus.

- Etiology
  - **Telescoping** of bowel; most **ileal-colic**
  - Most present at age 3 months to 6 years (80% <2 years)
  - Commonly **following adenovirus or rotavirus** infection, upper respiratory infection, otitis media
  - Associated with HSP (Henoch-Schönlein purpura)
  - Can also occur with a **leading point**—Meckel diverticulum, polyp, neurofibroma, hemangioma, malignancy
- Pathophysiology—bowel drags mesentery with it and produces arterial and venous obstruction and mucosal necrosis → classic **"black currant jelly" stool**

- Clinical presentation
  - **Sudden onset of severe paroxysmal colicky abdominal pain; straining, legs flexed**
  - **Progressive weakness**
  - **Lethargy, shock with fever**
  - Vomiting in most (early on, it is bile-stained)
  - Decreased stooling
  - Blood in most patients in first 12 hours, but may be delayed or not at all
- Physical examination—slightly tender, **sausage-shaped mass on right in cephalocaudal axis**
- Diagnosis
  - Ultrasound to first screen for the diagnosis (non-invasive and cost-effective; "doughnut appearance") and look for free-air (if intussusception has caused perforation)
  - Air enema is the next study of choice as it is far safer than the previously-used barium enema (0.1 vs. 2.5% risk of perforation); air enema may be therapeutic and prevent the need for immediate surgery
- Treatment
  - If prolonged, shock, peritoneal irritation, or perforation → surgery
  - **Radiographic reduction under fluoroscopy**—most will reduce if done within 48 hours of presentation (goes down to half after that time)
  - If surgical—**if manual operative reduction is not possible or bowel is not viable, then resection and end-to-end anastomosis**

Note

Other causes of GI bleed

- Anal fissure (most common cause of lower GI bleed in infancy)
- Accidental swallowing of maternal blood (do Apt test)
- Peptic ulcer disease

CONSTIPATION

Functional Constipation

A 6-year-old boy complains of hard bowel movements every fifth day. Physical examination reveals normal weight and height. Abdomen is soft, and hard stool is palpable on rectal examination.

- Delay or difficulty in stooling for at least 2 weeks; typically after age 2 years
- Passage of painful bowel movements with **voluntary withholding** to avoid pain
- May have blood in stool
- Physical examination—**large volume of stool palpated in suprapubic area; rectal exam shows vault filled with stool**
- Treatment
  - Patient education (**bowel training program**)
  - **Relief of impaction**—enema, then stool softeners (mineral oil, lactulose, polyethylene glycol; no prolonged use of stimulants)
  - Behavioral modification
  - Deal with any psychosocial issues

Hirschsprung Disease

- Etiology—absence of a ganglion cells in bowel wall beginning at internal anal sphincter and extending variably proximally
- **Most common reason for bowel obstruction in neonates**
- Clinical presentation
  - Symptoms usually present at birth
  - **Suspect in any full-term infant with a delay in passage of meconium (>24 hours)**
  - May have subsequent history of chronic constipation (if short aganglionic segment)
- Diagnosis
  - Rectal suction biopsy is definitive
  - Presence of **transition zone** on barium enema (not necessary to perform)
- Treatment—**surgery** (most with temporary colostomy) and wait 6–12 months for definitive correction (most achieve continence) or one-stage repair
- Complications—enterocolitis

Table 14-5. Functional Constipation Versus Hirschsprung Disease

	Functional Constipation	Hirschsprung Disease
Onset constipation	After 2 years of age	At birth
Failure to thrive	Uncommon	Possible
Enterocolitis	No	Possible
Abdominal distention	Usually not	Yes
Poor weight gain	Usually not	Common
Anal tone	Normal	Normal
Rectal	Stool in ampulla	No stool
Anorectal manometry	Distention of rectum → relaxation of internal sphincter	No sphincter relaxation
Barium enema	Large amount of stool; no transition zone	Transition zone with delayed evacuation

Renal and Urologic Disorders 15

Learning Objectives

- ❑ Recognize and describe treatment for urinary tract infection, vesicoureteral reflux, obstructive uropathy, and polycystic kidney disease
- ❑ Diagnose and describe treatments for disorders presenting with hematuria or proteinuria

URINARY TRACT INFECTION (UTI)

A 12-day-old infant presents with fever of 39 C (102 F), vomiting, and diarrhea. On physical examination the infant appears to be ill and mildly dehydrated.

- Epidemiology and risk factors
  - Age <24 months
    - 7% of febrile infants without a source and T >39 C (>102 F) for 24–48 hrs
    - More common in whites than blacks
    - Febrile females are more common in first year than age >12 mos
    - Male infection correlated to not being circumcised
  - Age ≥24 months
    - Can describe symptoms and localize
    - Most important factors: presence of bowel/bladder withholding behaviors; congenital anomalies; previous history of UTI
- Etiology and pathogenesis
  - *E. coli* is number 1 organism for all ages; then *Klebsiella, Proteus Enterococcus, Pseudomonas* (these all with later, recurrent infections and immune compromise)
  - Most from ascending infection; rare hematogenous spread
- Clinical presentation
  - Age <24 mos: fever, irritability, crying, decreased input, less sleep
  - Age ≥24 mos: localized symptoms of dysuria, urgency, frequency, suprapubic pain, incontinence for cystitis and abdominal or flank pain, malaise, nausea, vomiting, diarrhea for pyelonephritis
  - May also have asymptomatic bacteriuria–positive urine culture without signs or symptoms; may become symptomatic if untreated; almost exclusively in girls

- Diagnosis
  - Need evidence of **inflammation (urinalysis: WBCs and leukocyte esterase)** + **bacterial growth (UA nitrites, bacteria and positive culture)**
  - Age <24 mos: may place a urethral bag for UA only and then if positive → need catheterization for culture and sensitivity
  - **Age** ≥24 mos: mid-stream clean catch urine
  - **Best sensitivity and specificity for positive cultures: leukocyte esterase + nitrites + microscopic WBCs + microscopic bacteria**
  - Interpretation: ≥50,000 CFU/ml (may be less in neonates, immune deficiency, congenital anomalies or if already on antibiotics)
- Management
  - Oral antibiotics are as effective as IV
  - Use IV if toxic or cannot tolerate oral
  - Choice is tailored to local bacterial susceptibility data, compliance, cost and history of previous treatment/results
  - Oral: amoxicillin, trimethoprim-sulfamethoxazole, oral cephalosporins
  - Parenteral: best/safest are third-generation cephalosporins
- Imaging
  - Age <24 mos: renal and bladder U/S after first febrile UTI; VCUG after first febrile UTI with an abnormal U/S (note: not afebrile)
  - All children: **VCUG** after second febrile UTI (no policy for U/S or nonfebrile UTIs, which generally means that physicians should use their judgement)
  - If there is grade 2-5 reflux, obtain a renal radionuclide scan for function, kidney size, and scarring

Clinical Recall

Which of the following children should undergo a voiding cystourethrogram?

A. A 4-month-old uncircumcised male infant with his first positive urine culture

B. A 9-year-old girl with no significant medical history being treated for pyelonephritis

C. A 17-year-old sexually active girl with 2 urinary tract infections in 3 years

D. A 1-year-old boy with hydronephrosis on renal U/S

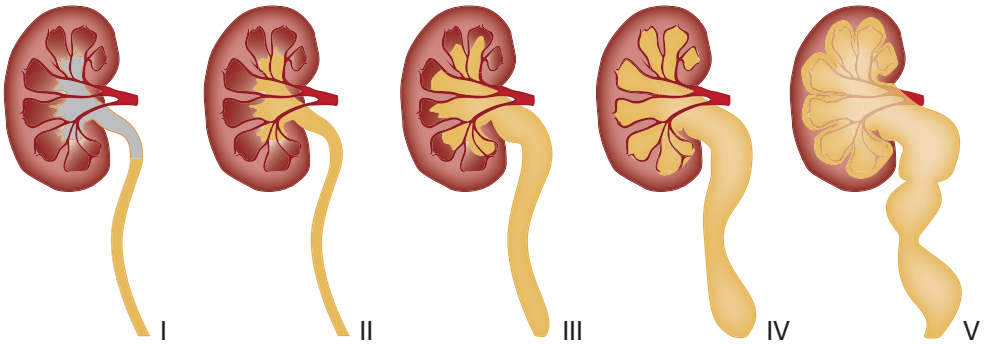
E. None of the above, as only children with recurrent UTIs should receive a VCUG

Answer: D

VESICOURETERAL REFLUX (VUR)

A 2-year-old girl presents with urinary tract infection. She has had multiple urinary tract infections since birth but has never had any follow-up studies to evaluate these infections. Physical examination is remarkable for an ill-appearing child who has a temperature of 40 C (104 F) and is vomiting.

- Definition—abnormal backflow of urine from bladder to kidney
- Etiology
  - Occurs when the submucosal tunnel between the mucosa and detrusor muscle is short or absent.
  - **Predisposition to pyelonephritis → scarring → reflux nephropathy (hypertension, proteinuria, renal insufficiency to end-stage renal disease [ESRD], impaired kidney growth)**
- Grading—see Figure 15-3
- Diagnosis
  - **VCUG for diagnosis and grading**
  - **Renal scan for renal size, scarring and function; if scarring, follow creatinine**
- Natural history
  - Increased scarring with grade V (less so with bilateral 4)
  - Most below grade V resolve regardless of age at diagnosis or whether it is unilateral or bilateral
  - With growth, tendency to resolve (lower > higher grades); resolve by age 6–7 years
- Treatment
  - Medical—based on reflux resolving over time; most problems can be taken care of **nonsurgically**
  - Careful ongoing monitoring for and aggressive treatment of all UTIs
  - Surgery if medical therapy fails, if grade V reflux, or if any worsening on VCUG or renal scan
  - The issue of antibiotic prophylaxis is controversial and thus must be individualized. Studies do show, however, that it would take thousands of doses of antibiotics to prevent a single UTI and that prophylaxis does not prevent scarring. Therefore, it is not currently recommended routinely by the AAP.



GRADE	DESCRIPTION
I	Reflux into a nondilated ureter
II	Reflux into the pelvis and calyces without dilation
III	Reflux with mild to moderate dilation of the ureter, renal pelvis, and calyces, with minimal blunting of the fornices
IV	Reflux with moderate tortuosity of the ureter and dilation of the pelvis and calyces
V	Reflux causing ureteral tortuosity with severe dilation of ureter, renal pelvis, and calyces and loss of fornices and papillary impressions

Figure 15-1. Vesicoureteral Grading Scale

OBSTRUCTIVE UROPATHY

- Definition—obstruction of urinary outflow tract
- Clinical presentation
  - **Hydronephrosis**
  - Upper abdominal or flank pain
  - Pyelonephritis, UTI (recurrent)
  - Weak, decreased urinary stream
  - Failure to thrive, diarrhea (or other nonspecific symptoms)
- Diagnosis
  - **Palpable abdominal mass in newborn; most common cause is hydronephrosis** due to ureteropelvic junction obstruction or **multicystic kidney disease** (less so–infantile polycystic disease)
  - **Most can be diagnosed prenatally with ultrasound.**
  - **Obtain VCUG in all cases of congenital hydronephrosis and in any with ureteral dilatation to rule out posterior urethral valves**
- Common etiologies
  - **Ureteropelvic junction obstruction—most common** (unilateral or bilateral hydronephrosis)
  - Ectopic ureter—drains outside bladder; causes continual incontinence and UTIs

  - Ureterocele—cystic dilatation with obstruction from a pinpoint ureteral orifice; mostly in girls
  - **Posterior urethral valves:**
    - **Most common cause of severe obstructive uropathy; mostly in boys**
    - **Can lead to end-stage renal disease**
    - **Present with mild hydronephrosis to severe renal dysplasia; suspect in a male with a palpable, distended bladder and weak urinary stream**
- Diagnosis—voiding cystourethrogram (VCUG)
- Treatment
  - Decompress bladder with catheter
  - Antibiotics (intravenously)
  - Transurethral ablation or vesicostomy
- Complications
  - If lesion is severe, may present with pulmonary hypoplasia (Potter sequence)
  - Prognosis dependent on lesion severity and recovery of renal function

DISEASES PRESENTING PRIMARILY WITH HEMATURIA

Acute Poststreptococcal Glomerulonephritis

A 10-year-old boy presents with Coca-Cola–colored urine and edema of his lower extremities. On physical examination, the patient has a blood pressure of 185/100 mm Hg. He does not appear to be in any distress. His lungs are clear to auscultation, and his heart has a regular rate and rhythm without any murmurs, gallops, or rubs. His past medical history is remarkable for a sore throat that was presumed viral by his physician 2 weeks before.

- Etiology
  - **Follows infection with nephrogenic strains of group A beta-hemolytic streptococci of the throat (mostly in cold weather) or skin (in warm weather)**
  - Diffuse mesangial cell proliferation with an increase in mesangial matrix; **lumpy-bumpy deposits of immunoglobulin (Ig) and complement** on glomerular basement membrane and in mesangium
  - Mediated by immune mechanisms but complement activation is mostly through the alternate pathway
- Clinical presentation
  - Most 5–12 years old (corresponds with typical age for strep throat)
  - **1–2 weeks after strep pharyngitis or 3–6 weeks after skin infection (impetigo)**
  - Ranges from asymptomatic microscopic hematuria to acute renal failure
  - **Edema, hypertension, hematuria (classic triad)**
  - Constitutional symptoms—malaise, lethargy, fever, abdominal or flank pain
- Diagnosis
  - Urinalysis—RBCs, **RBC casts**, protein 1–2 +, polymorphonuclear cells
  - Mild normochromic anemia (hemodilution and low-grade hemolysis)

Note

For diagnosis of prior Strep infection, use streptozyme (slide agglutination), which detects antibodies to streptolysin O, DNase B, hyaluronidase, streptokinase, and nicotinamide-adenine dinucleotidase.

  - **Low C3** (returns to normal in 6–8 weeks)
  - **Need positive throat culture or increasing antibody titer to streptococcal antigens; best single test is the anti-DNase antigen**
  - Consider biopsy only in presence of acute renal failure, nephrotic syndrome, absence of streptococcal or normal complement; or if present >2 months after onset
- Complications
  - Hypertension
  - Acute renal failure
  - Congestive heart failure
  - Electrolyte abnormalities
  - Acidosis
  - Seizures
  - Uremia
- Treatment (in-patient, if severe)
  - Antibiotics for 10 days (penicillin)
  - Sodium restriction, diuresis
  - Fluid and electrolyte management
  - Control hypertension (calcium channel blocker, vasodilator, or angiotensin-converting enzyme inhibitor)
  - Complete recovery in >95%

Other Glomerulonephritides

IgA nephropathy (Berger disease)

- **Most common chronic glomerular disease worldwide**
- Clinical presentation
  - Most commonly presents with gross hematuria **in association with upper respiratory infection** or gastrointestinal infection
  - Then mild proteinuria, mild to moderate hypertension
  - **Normal C3**
- Most important primary treatment is blood pressure control.

Alport syndrome

The school nurse refers a 7-year-old boy because he failed his hearing test at school. The men in this patient's family have a history of renal problems, and a few of his maternal uncles are deaf. A urinalysis is obtained from the patient, which shows microscopic hematuria.

- Hereditary nephritis (X-linked dominant); renal biopsy shows **foam cells**
- Asymptomatic hematuria and intermittent gross hematuria **1–2 days after upper respiratory infection**

- **Hearing deficits (bilateral sensorineural, never congenital);** females have subclinical hearing loss
- **Ocular abnormalities (pathognomonic is extrusion of central part of lens into anterior chamber**

Hemolytic uremic syndrome (HUS)

A 3-year-old child presents to the emergency center with history of bloody diarrhea and decreased urination. The mother states that the child's symptoms began 5 days ago after the family ate at a fast-food restaurant. At that time the patient developed fever, vomiting, abdominal pain, and diarrhea. On physical examination, the patient appears ill. He is pale and lethargic.

- **Most common cause of acute renal failure in young children**
- **Microangiopathic hemolytic anemia, thrombocytopenia, and uremia**
- Most from *E. coli* O157:H7 (shiga toxin–producing)
  - Most from undercooked meat or unpasteurized milk; spinach
  - Also from **Shigella, Salmonella, Campylobacter**, viruses, drugs, idiopathic
- Pathophysiology
  - Subendothelial and mesangial deposits of granular, amorphous material—vascular occlusion, glomerular sclerosis, cortical necrosis
  - Capillary and arteriolar endothelial injury → **localized clotting**
  - **Mechanical damage to RBCs as they pass through vessels**
  - **Intrarenal platelet adhesion and damage** (abnormal RBCs and platelets then removed by liver and spleen)
  - Hypercoagulable state
- Clinical presentation
  - Most common <4 years old
  - Bloody **diarrhea**
  - **5–10 days after infection, sudden pallor, irritability, weakness, oliguria occur; mild renal insufficiency to acute renal failure** (ARF)
- Labs—hemoglobin 5–9 mg/dL, **helmet cells, burr cells, fragmented cells,** moderate reticulocytosis, white blood cells up to 30,000/mm^3, Coombs negative, **platelets usually 20,000–100,000/mm^3,** low-grade microscopic hematuria and proteinuria
- Many complications, including seizures, infarcts, colitis, intussusception, perforation heart disease, death

- Treatment
  - Meticulous attention to fluids and electrolytes
  - Treat hypertension
  - Aggressive nutrition (total parenteral nutrition [TPN])
  - Early peritoneal dialysis
  - **No antibiotics if *E. coli* O157:H7 is suspected—treatment increases risk of developing HUS**
  - Plasmapheresis or fresh frozen plasma—may be beneficial in HUS **not** associated with diarrhea or with severe central nervous system involvement
- Prognosis—more than 90% survive acute stage; small number develop ESRD (end-stage renal disease)

Clinical Recall

A 15-year-old girl recovering from the common cold presents with gross hematuria, causing red blood cell casts and mild proteinuria on urinalysis. There are no hearing difficulties and eye exam is normal. What is the treatment of choice?

A. No treatment beyond control of blood pressure

B. Penicillin

C. Steroids

D. NSAIDs

E. Plasmapheresis

Answer: A

POLYCYSTIC KIDNEY DISEASE

Autosomal-Recessive Type (Infantile)

- Both kidneys **greatly enlarged** with many cysts through cortex and medulla
- **Microcysts** → development of **progressive interstitial fibrosis and tubular atrophy** → **renal failure**
- Also **liver disease**—bile duct proliferation and ectasia with hepatic fibrosis
- Clinical presentation
  - Bilateral flank masses in neonate or early infancy
  - May **present with Potter sequence**
  - Hypertension, oliguria, acute renal failure
  - About half have liver disease in newborn period
- Diagnosis
  - **Bilateral flank masses in infant with pulmonary hypoplasia (if severe)**
  - Oliguria and hypertension in newborn with absence of renal disease in parents
  - Ultrasound–prenatal and postnatal (numerous small cysts throughout)

- Treatment and prognosis
  - Symptomatic
  - Now more than 80% with 10-year survival
  - End-stage renal failure in more than half
  - **Need dialysis and transplant**

Autosomal-Dominant Type (Adults)

- **Most common hereditary human kidney disease**
- Both kidneys enlarged with cortical and medullary cysts
- Most present in **fourth to fifth decade,** but may present in children and neonates
- Renal ultrasound shows bilateral **macrocysts**
- Also **systemic cysts**—liver, pancreas, spleen, ovaries; **intracranial (Berry) aneurysm** (rarely reported in children)
- Diagnosis—**presence of enlarged kidneys with bilateral macrocysts with affected first-degree relative**
- Treatment—**control of blood pressure** (disease progression correlates with degree of hypertension); presentation in older children with favorable prognosis

DISEASES PRESENTING WITH PROTEINURIA

Nephrotic Syndrome

A 3-year-old child presents to the physician with a chief complaint of puffy eyes. On physical examination, there is no erythema or evidence of trauma, insect bite, cellulitis conjunctival injection, or discharge.

- **Steroid-sensitive minimal change disease is the most common nephrotic syndrome seen in children.**
- Features
  - **Proteinuria (>40 mg/m^2/hour)**
  - **Hypoalbuminemia (<2.5 g/dL)**
  - **Edema**
  - **Hyperlipidemia (reactive to loss of protein)**

Minimal change disease

- Clinical presentation
  - **Most common between 2 and 6 years of age**
  - May follow minor infections
  - **Edema**—localized initially around eyes and lower extremities; anasarca with serosal fluid collections less common
  - Common—diarrhea, abdominal pain, anorexia
  - Uncommon—hypertension, gross hematuria

- Diagnosis
  - Urinalysis shows proteinuria (3–4 +)
  - Some with **microscopic hematuria**
  - 24-hour urine protein—**40 mg/m^2/hour in children but now preferred initial test is a spot urine for protein/creatinine ratio >2**
  - **Serum creatinine usually normal** but may be increased slightly
  - **Serum albumin <2.5 g/dL**
  - **Elevated serum cholesterol and triglycerides**
  - **C3 and C4 normal**
- Treatment
  - Mild—outpatient management; **if severe—hospitalize**
  - Start **prednisone** for 4–6 weeks, then taper 2–3 months without initial biopsy
  - **Consider biopsy with hematuria, hypertension, heart failure, or if no response after 8 weeks of prednisone (steroid resistant)**
  - Sodium restriction
  - If severe—fluid restriction, plus intravenous 25% albumin infusion, followed by diuretic to mobilize and eliminate interstitial fluid
  - Re-treat relapses (may become steroid-dependent or resistant); may use alternate agents (cyclophosphamide, cyclosporine, high-dose pulsed methylprednisolone); renal biopsy with evidence of steroid dependency
- Complications
  - **Infection is the major complication**; make sure immunized against *Pneumococcus* and *Varicella* and check PPD
  - **Most frequent is spontaneous bacterial peritonitis (*S. pneumoniae* most common)**
  - Increased risk of thromboembolism (increased prothrombotic factors and decreased fibrinolytic factors) but really with aggressive diuresis
- Prognosis
  - Majority of children have **repeated relapses; decrease in number with age**
  - Those with steroid resistance and who have focal segmental glomerulosclerosis have much poorer prognosis (progressive renal insufficiency).

MALE GENITOURINARY DISORDERS

Undescended Testes

Note

Differentiate **undescended testes** from **retractile testes** (brisk cremasteric reflect age >1 [can manipulate into scrotum]).

- **Most common disorder of sexual differentiation in boys (more in preterm)**
- Testes should be descended by **4 months** of age or will remain undescended
- Usually in inguinal canal, but some are ectopic
- Prognosis
  - Treated: bilateral (50–65% remain fertile), unilateral (85% remain fertile)
  - Untreated or delay in treatment: increased risk for **malignancy (seminoma** most common)
- **Surgery (orchiopexy) at 9–15 months**

Testicular Torsion

- **Most common cause of testicular pain age >12 years**
- Clinical presentation—**acute pain and swelling; tenderness to palpitation**
- Testicle in transverse lie and retracted, no cremasteric reflex
- Diagnosis—Doppler color flow ultrasound (only to determine direction of torsion in order to guide manual detorsion, if urologist decides this is warranted; also to confirm successful detorsion in a completely asymptomatic patient)
- Treatment—**emergent surgery** (scrotal orchiopexy); if within 6 hours and <360-degree rotation, >90% of testes survive

Torsion of Appendix Testes

- **Most common cause of testicular pain age 2–11 years**
- Clinical presentation
  - **Gradual onset**
  - 3–5 mm, tender, inflamed mass at **upper pole of testis**
  - Naturally resolves in 3–10 days (bed rest, analgesia)
- Diagnosis
  - Clinical—**blue dot** seen through scrotal skin
  - Ultrasound if concerned with testicular torsion
  - Scrotal exploration if diagnosis still uncertain

Epididymitis

- **Ascending, retrograde urethral infection → acute scrotal pain and swelling (rare before puberty)**
- **Main cause of acute painful scrotal swelling in a young, sexually active man**
- Urinalysis shows **pyuria** (can be *Chlamydia* or *N. gonorrhoeae* [GC], but organisms mostly undetermined)
- Treatment—**bed rest and antibiotics**

Testicular Tumors

- 65% are malignant
- Palpable, hand mass that **does not** transilluminate
- Usually **painless**
- Diagnosis
  - Ultrasound
  - Serum AFP, beta-HCG (markers for germ cell tumors)
- Treatment—radical orchiectomy

Endocrine Disorders 16

Learning Objectives

- ❑ Recognize and describe treatments for thyroid, parathyroid, and adrenal disorders
- ❑ Describe the epidemiology and treatment of childhood diabetes mellitus

PITUITARY DISORDERS

Hypopituitarism

- **Deficiency of growth hormone ± other hormones; also delay in pubertal development is common; results in postnatal growth impairment corrected by growth hormone**
- Isolated growth-hormone deficiency or multiple pituitary deficiencies
  - Congenital—autosomal dominant, recessive, or X-linked recessive
  - Acquired—any lesion that damages the hypothalamus, pituitary stalk, or anterior pituitary **(most common is craniopharyngioma)**
- Clinical presentation
  - **Congenital** hypopituitarism:
    - **Normal size and weight at birth; then severe growth failure in first year**
    - Infants—**present with neonatal emergencies**, e.g., apnea, hypoglycemic seizures, hypothyroidism, hypoadrenalism in first weeks or boys with microphallus and small testes ± cryptorchidism
    - Also have a variety of dysmorphic features; appearance
  - **Acquired** hypopituitarism:
    - Findings appear gradually and progress: growth failure; pubertal failure, amenorrhea; symptoms of both decreased thyroid and adrenal function; possible DI
    - If there is an **expanding tumor**: headache, vomiting; visual changes, decreased school performance; papilledema, cranial nerve palsies
- Laboratory evaluation
  - Screen for **low serum insulin-like growth factor (IGF)-1 and IGF-binding protein-3 (IGF-BP3)**
  - Definitive test—**growth-hormone stimulation test**
  - **Examine other pituitary function:**
    - Thyroid-stimulating hormone (TSH), T_4
    - Adrenocorticotropic hormone (ACTH), cortisol, dehydroepiandrosterone (DHEA) sulfate, gonadotropins, and gonadal steroids

Note

If there is a normal response to hypothalamic-releasing hormones, the pathology is located within the hypothalamus.

- Other studies
  - X-ray most helpful with **destructive lesions** (enlargement of sella, erosions)
  - Calcification
  - **Bone age—skeletal maturation markedly delayed (BA 75% of CA)**
  - **MRI is indicated in all patients with hypopituitarism** (superior to CT scan)
- Differential diagnoses (the major ones)
  - **Systemic conditions** (Weight is often proportionally much less than height.)
  - **Constitutional delay** (delayed BA, delayed adolescent growth spurt, and pubertal development)
  - Familial **short stature** (BA = CA, short parents)
  - **Primary hypothyroidism**
  - **Emotional deprivation** (psychosocial dwarfism)
- Treatment
  - Classic growth-hormone deficiency—**recombinant growth hormone**
  - Need periodic thyroid evaluation—develop reversible hypothyroidism
- Indications—**growth hormone currently approved in United States for**
  - Documented growth-hormone deficiency
  - Turner syndrome
  - End-stage renal disease before transplant
  - Prader-Willi syndrome
  - Intrauterine growth retardation (IUGR) without catch-up growth by 2 years of age
  - Idiopathic pathologic short stature

Hyperpituitarism

Note

If the history suggests anything other than familial tall stature or obesity, or if there are positive physical findings, then the patient needs laboratory evaluation.

- Primary—**rare;** most are hormone-secreting **adenomas**
- Majority are deficiencies of target organs and because of negative feedback, there are increases in hypothalamus and pituitary hormones
- Laboratory evaluation
  - Screen—**IGF-1 and IGF-BP3 for growth hormone excess;** confirm with a glucose suppression test
  - **Need MRI of pituitary**
  - **Chromosomes especially in tall males** (decreased upper- to lower-body segment ratio suggests XXY; intellectual disability suggests fragile X)
  - **Thyroid tests**
- Management
  - Treatment only if prediction of adult height (based on BA) >3 SD above the mean or if there is evidence of severe psychosocial impairment
  - Trial of sex steroids (accelerates puberty and epiphyseal fusion)

Prolactinoma

- Most common pituitary disorder of adolescents; more common in girls
- Headache, visual disturbances (with large tumors), galactorrhea, amenorrhea ± findings of hypopituitarism (again with large tumors)
- Diagnosis: increased serum prolactin level then best test, MRI
- Treatment: bromocriptine (still the only dopamine-agonist approved for children)

Physiologic Gynecomastia

- Breast tissue in the male: common (estrogen: androgen imbalance)
- Distinguish from pseudogynecomastia: adipose tissue in an overweight male
- May occur in newborns (estrogen effect) or adolescents (most common)
- Symmetric or asymmetric; may be tender
- Usually up to age 2 years
- If significant with psychological impairment, consider danazol (anti-estrogen) or surgery (rare)

Precocious Puberty

- Definition
  - Girls—sexual development age <8 years
  - Boys—sexual development age <9 years
- Most common etiologies
  - Sporadic and familial in girls
  - Hamartomas in boys
- Clinical presentation—advanced height, weight, and bone age; early epiphyseal closure and early/fast advancement of Tanner stages
- Evaluation
  - Screen—significant increase in luteinizing hormone
  - Definitive—GnRH stimulation test; give intravenous GnRH analog for a brisk, luteinizing hormone response
  - If positive, then order MRI
- Treatment—stop sexual advancement and maintain open epiphyses (stops BA advancement) with leuprolide

Incomplete Precocious Puberty

- Premature thelarche
  - Usually isolated, transient (from birth due to maternal estrogens)
  - May be first sign of true precocious puberty
- Premature adrenarche—early adrenal androgen production (variation of normal)—axillary, inguinal, and genital hair. It is familial.
- Premature menarche—very rare (other causes of bleeding much more common)

Clinical Recall

A 7-year-old boy is seen by his pediatrician and noted to be Tanner Stage 3. Initial work-up reveals no oncologic process. What is the treatment of choice?

A. Growth hormone

B. Bromocriptine

C. Leuprolide

D. Thyroid hormone

E. Surgical resection of the testicles

Answer: C

THYROID DISORDERS

Hypothyroidism

A 2-month-old patient appears to be having inadequate weight gain. His mother states he is constipated. On examination, he has decreased muscle tone, a large fontanel, a large tongue, and an umbilical hernia.

- *Congenital* hypothyroidism—**most are primary** (i.e., from thyroid gland)
  - Sporadic or familial; **with or without a goiter**
    - Most common is **thyroid dysgenesis** (hypoplasia, aplasia, ectopia); **no goiter**
    - Defect in **thyroid hormone synthesis—goitrous**; autosomal recessive
    - **Transplacental passage of maternal thyrotropin** (transient)
    - Exposure to maternal antithyroid drugs
    - Radioiodine exposure/fetal exposure to excessive iodine (topical iodine antiseptics) (now rare in U.S.)
    - Iodine deficiency or endemic goiter
    - Central hypopituitarism
  - Clinical presentation is known as "cretinism."
    - **Prolonged jaundice**
    - **Large tongue**
    - **Umbilical hernia**
    - **Edema**
    - **Intellectual disability; developmental delay**
    - **Anterior and posterior fontanels wide**
    - **Mouth open**
    - **Hypotonia**
  - Other findings—weight and length normal at birth, feeding difficulties, apnea, sluggish, decreased appetite, increased sleep, constipation, decreased temperature, skin cold and mottled, peripheral anemia; apathetic appearance

  - Laboratory evaluation:
    - **Low serum T_4 or free T_4; increased TSH**
  - Treatment—**sodium thyroxine**
- *Acquired* hypothyroidism
  - **Hashimoto**; thyroiditis is most common cause; may be part of **autoimmune polyglandular syndrome**
  - Typically presents in **adolescence**
  - Other causes—iatrogenic (medications, irradiation, surgery, radioiodine); systemic disease (cystinosis, histiocytic infiltration)
- Clinical presentation
  - Many more girls than boys
  - **First sign usually deceleration of growth**
  - Then myxedema, constipation, cold intolerance, decreased energy, increased sleep, delayed osseous maturation, delayed puberty, headache, visual problems
  - **Diffusely increased, firm, nontender thyroid;** but may be atrophic so can be nongoitrous
  - Laboratory and treatment—same as congenital

Hyperthyroidism

A 12-year-old girl has a 6-month history of hyperactivity and declining school performance. Appetite is increased, but she shows no weight gain. Physical examination reveals a slight tremor of the fingers, mild exophthalmos, and a neck mass.

- Almost all cases are **Graves disease**
- **Peak at age 11–15 years;** girls > boys
- **Most with family history** of some form of autoimmune thyroid disease
- Findings
  - **Infiltration of thyroid and retro-orbital tissue** with lymphocytes and plasma cells → exophthalmos
  - **Lymphadenopathy and splenomegaly**
  - Thymic hyperplasia
- In whites, association with HLA-B8 and **DR3** is also seen with other DR3-related disorders (Addison disease, diabetes mellitus, myasthenia gravis, celiac disease).
- Clinical
  - Most signs and symptoms appear **gradually**
  - Earliest **usually emotional lability and motor hyperactivity**
  - **Decreased school performance**, tremor, increased appetite with weight loss, skin flushed with increased sweating, muscle weakness, **tachycardia, palpitations, arrhythmias, hypertension**
  - **Goiter, exophthalmos**
  - **Thyroid storm**—acute onset of hyperthermia, severe tachycardia, restlessness → rapid progression to delirium, coma, and death
- Laboratory evaluation
  - **Increased T_4, T_3, free T_4**
  - **Decreased TSH**
  - Measurable TRS-AB (and may have thyroid peroxidase antibodies)

Note

Autoimmune Polyglandular Disease

Type I

- Hypoparathyroidism
- Addison disease
- Mucocutaneous candidiasis
- Small number with autoimmune thyroiditis

Type II *(Schmidt syndrome)*

- Addison disease, *plus*:
- Insulin-dependent DM
- With or without thyroiditis

Note

Thyroid cancer in children is uncommon, but you should know about medullary carcinoma (parafollicular cells), seen in 2 of the multiple endocrine neoplasias (MEN):

- **MEN IIA:** hyperplasia or cancer of thyroid ***plus*** adrenal medullary hyperplasia or pheochromocytoma ***plus*** parathyroid hyperplasia
- **MEN IIB (mucosal neuroma syndrome):** multiple neuromas ***plus*** medullary thyroid cancer ***plus*** pheochromocytoma

- Treatment
  - **Propylthiouracil (PTU) or methimazole**
  - **Beta blockers** for acute symptoms (thyroid storm)
  - If medical treatment not adequate, radioablation or surgery; then treat as hypothyroid (daily thyroxine replacement)

PARATHYROID DISORDERS

Hypoparathyroidism

- Parathyroid hormone (PTH) deficiency
- Etiologies—most due to DiGeorge syndrome or velocardiofacial syndrome (aplasia/hypoplasia); remainder are defects involving production of parathyroid hormone (X-linked recessive, autosomal dominant) and postsurgical, autoimmune, and idiopathic defects
- Clinical presentation—early onset of muscle pain/cramps, numbness, and tingling; then laryngeal and/or carpopedal spasm; and finally seizures, with very low calcium (common initial presentation of DiGeorge)
- Laboratory evaluation
  - **Decreased serum calcium** (5–7 mg/dL)
  - **Increased serum phosphorus** (7–12 mg/dL)
  - Normal or low alkaline phosphatase
  - Low 1,25 $[OH]_2D_3$ (calcitriol)
  - Normal magnesium
  - **Low parathyroid hormone** (immunometric assay)
  - EKG: **prolongation of QT**
- Treatment
  - Emergency for neonatal tetany → intravenous 10% calcium gluconate and then 1,25$[OH]_2D_3$ (calcitriol); this normalizes the calcium
  - Chronic treatment with calcitriol or vitamin D2 (less expensive) *plus* adequate calcium intake (daily elemental calcium)
  - Decrease foods high in phosphorus (milk, eggs, cheese)

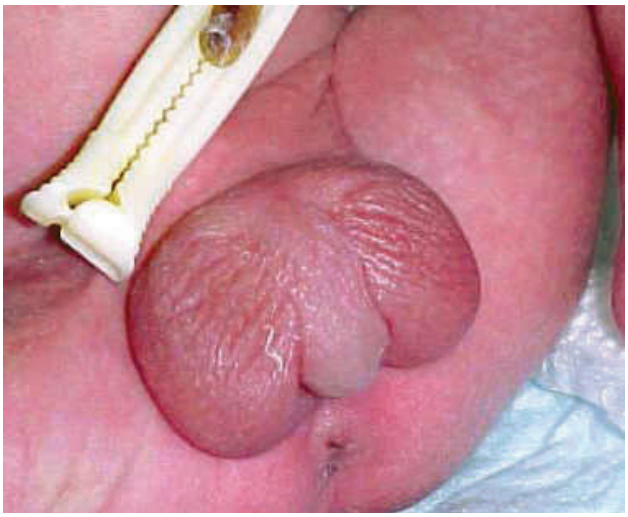
Table 16-1. Lab Diagnosis of Parathyroid Disease

	PTH	Calcium	Phosphate	Alkaline Phosphatase
Primary Hypo	Decreased	Low	High	Normal
Pseudo Hypo	Increased	Low	High	NL or SL increased
Primary Hyper	Increased	High	Low	Increased
Secondary Hyper	Increased	NL to SL decreased	Low	Huge increase

Vitamin D Deficiency

- Most common cause of rickets
- Poor intake, inadequate cutaneous synthesis
- Low serum phosphate, normal to low serum calcium lead to increased PTH and increased alkaline phosphatase
- Increased 25-hydroxy vitamin D
- Fractures, rachitic rosary, craniotabe bone deformities
- Treatment: initial vitamin D replacement and calcium, then adequate dietary calcium and phosphate

ADRENAL DISORDERS



TheFetus.net.

Figure 16-1. Ambiguous Genitalia Seen in Congenital Adrenal Hyperplasia

Congenital Adrenal Hyperplasia (CAH)

A 1-month-old infant is seen with vomiting and severe dehydration. Physical examination reveals ambiguous genitalia.

- **21-Hydroxylase deficiency (most common)**
  - Autosomal-recessive enzyme deficiency
  - Decreased production of cortisol → **increased ACTH** → **adrenal hyperplasia**
  - **Salt losing** (not in all cases; some may have normal mineralocorticoid synthesis)
  - Precursor steroids (17-OH **progesterone**) accumulate → pathway shunts to androgen synthesis → masculinized female external genitalia

Note

Other 3 Main Defects in CAH

- **3-beta-hydroxysteroid deficiency:** salt-wasting, male and female pseudohermaphrodites, precocious pubarche; increased 17-OH pregnenolone and DHEA
- **11-beta-hydroxylase deficiency:** female pseudohermaphroditism, postnatal virilization, hypertension; increased compound S, DOC, serum androgens, and hypokalemia
- **17-alpha hydroxyl/17,20 lyase deficiency:** male pseudohermaphroditism, sexual infantilism, hypertension; increased DOC, 18-OH DOC, 18-OH corticosterone, and 17-alpha-hydroxylated steroids; hypokalemia

  - Findings (with salt losing):
    - Progressive weight loss (through 2 weeks of age), anorexia, vomiting, dehydration, weakness, hypotension
    - **Affected females—masculinized external genitalia (internal organs normal)**
    - Males normal at birth; postnatal virilization
- Laboratory evaluation
  - **Increased 17-OH progesterone**
  - Low cortisol, increased androstenedione and testosterone
  - Hyperkalemia, hyponatremia, low aldosterone
  - High plasma renin activity (PRA), particularly the ratio of PRA to aldosterone (markers of impaired mineralocorticoid synthesis)
  - **Definitive test**—measure 17-OH progesterone before and after an intravenous bolus of ACTH
- Treatment
  - **Hydrocortisone**
  - **Fludrocortisone** if salt losing
  - **Increased doses of both hydrocortisone and fludrocortisone in times of stress**
  - Corrective surgery for females

Cushing Syndrome

- Exogenous—most common reason is **prolonged exogenous glucocorticoid administration.**
- Endogenous
  - In infants—**adrenocortical tumor (malignant)**
  - Excess ACTH from **pituitary adenoma** results in **Cushing disease** (age >7 years)
- Clinical findings
  - **Moon facies**
  - **Truncal obesity**
  - **Impaired growth**
  - **Striae**
  - **Delayed puberty and amenorrhea**
  - **Hyperglycemia**
  - Hypertension common
  - Masculinization
  - **Osteoporosis with pathologic fractures**
- Laboratory evaluation
  - **Dexamethasone-suppression test (single best test)**
  - **Determine cause—CT scan (gets most adrenal tumors) and MRI (may not see if microadenoma)**
- Treatment—remove tumor; if no response, remove adrenals; other tumor-specific protocols

Clinical Recall

What laboratory abnormality is expected in patients with 21-hydroxylase deficiency?

A. Hyperglycemia

B. Hyponatremia

C. Hypokalemia

D. High cortisol

E. High aldosterone

Answer: B

DIABETES MELLITUS

Type 1

An 8-year-old boy arrives in the emergency department with vomiting and abdominal pain of 2 days' duration. His mother states he has been drinking a lot of fluids for the past month and has lost weight. Physical examination reveals a low-grade fever and a moderately dehydrated boy who appears acutely ill. He is somnolent but asks for water. Respirations are rapid and deep. Laboratory tests reveal a metabolic acidosis and hyperglycemia.

- Etiology—T-cell–mediated autoimmune destruction of islet cell cytoplasm, insulin autoantibodies (IAA)
- Pathophysiology—low insulin **catabolic state**
  - Increased glucose production and decreased tissue utilization lead to increased serum glucose concentration → **osmotic diuresis (hyperosmotic state)**; result is a loss of fluid and electrolytes, and eventual dehydration
  - Activation of **renin-angiotensin-aldosterone axis** can lead to **accelerated potassium loss**
  - Increased catabolism → **cellular loss of Na, K and phosphate**
  - Increased release of **free fatty acids** from peripheral fat stores = substrates for **hepatic ketoacid production** → depleted buffer system → **metabolic acidosis**
- Clinical presentation
  - **Polyuria**
  - **Polydipsia**
  - **Polyphagia**
  - **Weight loss**
  - **Most initially present with diabetic ketoacidosis**

- Diagnostic criteria
  - Impaired glucose tolerance test: fasting blood sugar 110–126 mg/dL or 2-hour glucose during OGTT<200 mg/dL but ≥125 mg/dL
  - Diabetes: symptoms + random glucose ≥200 mg/dL or fasting blood sugar ≥126 mg/dL or 2 hour OGTT glucose ≥200 mg/dL
  - **Diabetic ketoacidosis—hyperglycemia, ketonuria, increased anion gap, decreased HCO_3 (or total CO_2), decreased pH, increased serum osmolality**
- Treatment
  - Insulin replacement—goal is to provide in as physiologic a manner as possible. Give basal insulin and a preprandial insulin. The basal insulin is either long-acting (glargine or detemir) or intermediate-acting (NPH).
  - American Diabetes Association—test blood sugar before meals and snacks, before bed, before exercising or driving, and with suspicion of low blood sugar
  - Dietary management—healthy, balanced diet (high in carbohydrates and fiber, low in fat)
  - Close patient follow-up
  - Diabetic ketoacidosis:
    - Most important **FIRST step:** start **insulin infusion** to accelerate the movement of glucose into cells → decreases hepatic glucose production + stops the movement of FFA from periphery to liver
    - **Begin rehydration** at the same time; also lowers serum glucose level by improving renal perfusion and renal excretion
    - There is a **rapid initial decrease in serum glucose**; when the glucose level is <180 mg/dL (**renal threshold**), diuresis stops and rehydration accelerates.
    - Rehydration is **slow**, 24–36 hours depending on severity of DKA. **Note:** A rapid decline in effective serum osmolality can represent an excess of free water entering the vascular space and increasing risk of **cerebral edema.**
  - Exercise
    - All forms of exercise or competitive sports should be encouraged.
    - Regular exercise improves glucose control.
    - May need additional CHO exchange

Type 2

- **Most common cause of insulin resistance is childhood obesity.**
- Symptoms more insidious
  - Usually excessive weight gain
  - Fatigue
  - Incidental glycosuria (polydipsia and polyuria uncommon)
- Risk factors
  - Age 10-19 years
  - Overweight to obese (BMI for age and sex >85%)
  - Non-Caucasian
  - History of type 2 DM in 1st- or 2nd-degree relatives
  - Having features of the metabolic syndrome

- Features of the Metabolic Syndrome
  - Glucose intolerance leads to L hyperglycemia
  - Insulin resistance
  - Obesity
  - Dyslipidemia
  - Hypertension
  - Acanthosis nigricans
- Screening and Treatment
  - **Who:** All who meet the BMI criteria + 2 risk factors
  - **How to screen:** fasting blood glucose every 2 years beginning at age 10 years or onset of puberty if above criteria are met
  - **Diagnosis:** same criteria (glucose levels) as adults
  - **Treatment:** first and most important is nutritional education and improved exercise level, but most will eventually need an oral hypoglycemic

Maturity-Onset Diabetes of Youth (MODY)

- Primary autosomal dominant defect in insulin secretion (6 types based on gene mutation)
- Diagnosis: 3 generations of DM with autosomal; dominant transmission and diagnosis of onset age <25 years
- Best test: molecular genetics for mutation (facilitates management and prognosis)

Orthopedic Disorders 17

Learning Objectives

- ❑ Recognize and describe treatments for childhood disorders of the hip, knee, foot, spine, and upper limbs
- ❑ Diagnose and describe treatments for osteomyelitis, septic arthritis, osteogenesis imperfecta, and bone tumors

DISORDERS OF THE HIP

Developmental Dysplasia of the Hip (DDH)

- General ligamental laxity
  - Family history
  - Significantly more females
  - Firstborn
  - Breech
  - Oligohydramnios
  - Multiple gestation
- Physical examination
  - **Barlow:** will dislocate an unstable hip; is easily felt (clunk not a click)
  - **Ortolani** (most important clinical test for detecting infant hip dysplasia): reduces a recently dislocated hip (most at 1–2 months of age), but after 2 months, usually not possible because of soft-tissue contractions
- All infants with positive exams should **immediately be referred to an orthopedic surgeon** (per standard of practice of the AAP); no radiographic confirmation is needed
- If equivocal, can repeat exam in 2 weeks and if equivocal then **a dynamic U/S** of the hips is the best test (age <4 months) or hip x-ray (age >4 months)
- Treatment
  - Pavlik harness for 1–2 months (highly effective)
  - Casting (if needed), surgery (rarely necessary)
- Complications—acetabular dysplasia, leg length discrepancy

Legg-Calvé-Perthes Disease

A 5-year-old boy has developed progressive limping. At first painless, it now hurts to run and walk. The pain is in the anterior thigh. The pain is relieved by rest. Parents recall no trauma.

- **Idiopathic avascular necrosis** of the **capital femoral epiphysis** in immature, growing child
- More in males; 20% bilateral; sometimes after trauma
- Presentation—mild intermittent pain in anterior thigh with **painless limp** with restriction of motion
- Diagnosis—anterior/posterior and frog leg lateral x-ray shows compression, collapse, and deformity of femoral head
- Treatment
  - Containment (femoral head within acetabulum) with orthoses or casting
  - Bed rest
  - Abduction stretching exercises
  - If significant femoral deformity persists, surgical correction

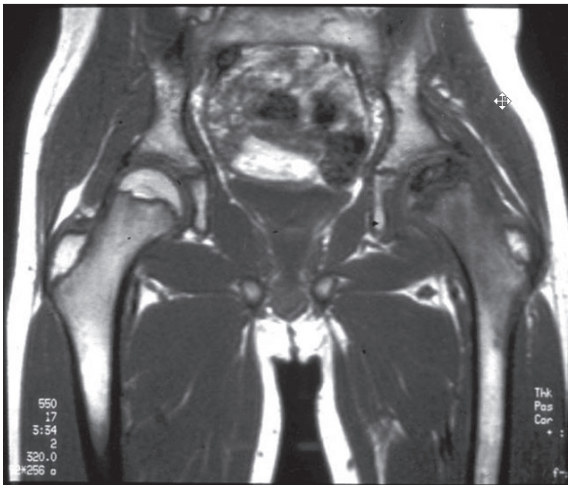


Figure 17-1. MRI Demonstrating Legg-Calve-Perthes Disease

Slipped Capital Femoral Epiphysis (SCFE)

- Most common adolescent hip disorder
- Either **obese** with delayed skeletal maturation, or **thin** with a **recent growth spurt**
- Can occur with an underlying endocrine disorder
- Clinical presentation
  - Pre-slip stable; exam normal; mild limp external rotation
  - Unstable slip; sudden-onset extreme pain; cannot stand or walk; 20% complain of knee pain with decreased hip rotation on examination

- Complications—osteonecrosis (avascular necrosis) and chondrolysis (degeneration of cartilage)
- Diagnosis—AP and frog-leg lateral x-ray, earliest finding: widening of physis without slippage (preslip); as slippage occurs, femoral neck rotates anteriorly while head remains in acetabulum
- Treatment—open or closed reduction (pinning)

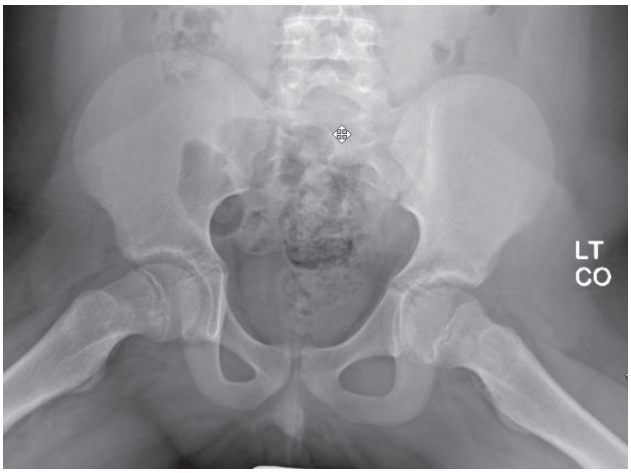


Figure 17-2. X-ray of the Hips Demonstrating Slipped Capital Femoral Epiphysis

Transient Synovitis

- Viral; most 7–14 days after a nonspecific upper respiratory infection; most at 3–8 years of age
- Clinical presentation
  - Acute mild pain with **limp** and mild restriction of movement
  - Pain in groin, anterior thigh, and knee
- Diagnosis
  - Small effusion (±)
  - Slight increase in ESR
  - **Normal x-rays**
  - No to low-grade fever; non-toxic-appearing
- Treatment—bed rest and no weight-bearing until resolved (usually <1 week), then 1–2 weeks of limited activities

Clinical Recall

A 12-year-old boy presents with a limp. He is overweight. Radiographs are concerning for slipped capital femoral epiphysis. What is the treatment of choice?

A. Pavlik harness
B. Surgical pinning
C. Casting and rest
D. Physical therapy
E. Antibiotics

Answer: B

INTOEING

Metatarsus Adductus

- Most common in firstborn (deformation)
- Treatment—primarily nonsurgical; serial plaster casts before 8 months of age; orthoses, corrective shoes; if still significant in a child age >4 years, may need surgery

Talipes Equinovarus (Clubfoot)

A newborn is noted to have a foot that is stiff and slightly smaller than the other one. The affected foot is medially rotated and very stiff, with medial rotation of the heel.

Note

In **talipes equinovarus**, the patient's heel can't go flat on the exam surface (as opposed to metatarsus adductus, in which the heel can).

- Congenital, positional deformation, or associated with neuromuscular disease
- Hindfoot equinus, hindfoot and midfoot varus, forefoot adduction (at talonavicular joint)
- Treatment
  - Complete correction should be achieved by 3 months (serial casting, splints, orthoses, corrective shoes); if not, then surgery

Internal Tibial Torsion

- **Most common cause of intoeing <2 years of age** (also because of in utero positioning); often with metatarsus adductus
- Measure prone thigh/foot angles
- No treatment needed—resolves with normal growth and development; takes 6–12 months (is physiologic)

Internal Femoral Torsion (Femoral Anteversion)

- Most common cause of intoeing ≥2 years of age; entire leg rotated inwardly at hip during gait
- Most are secondary to abnormal sitting habits (W-sitting).
- Treatment—observation; takes 1–3 years to resolve; surgery only if significant at >10 years of age

DISORDERS OF THE KNEE

Osgood-Schlatter Disease

- Traction apophysitis of tibial tubercle (**overuse injury**)
- Look for **active adolescent** (running, jumping)
- Swelling, tenderness, increased **prominence of tubercle**
- Treatment—**rest**, restriction of activities, knee immobilization, isometric exercises
- Complete resolution requires 12–24 months

DISORDERS OF THE SPINE

Scoliosis

A 12-year-old girl is seen for routine physical examination. She voices no complaints. Examination is remarkable for asymmetry of the posterior chest wall on bending forward. One shoulder appears higher than the other when she stands up.

- **Most are idiopathic**
- Others are congenital, with neuromuscular disorders, compensatory, or with intraspinal abnormalities.
- Slightly more females than males; more likely to progress in females
- Adolescent (**>11 years**) more common
- **Adams test bending forward at hips** —almost all with >**20-degree** curvature are identified in school screening programs (but many false positives)
- Diagnosis—x-ray is standard: posterior/anterior and lateral of entire spine gives greatest angle of curvature
- Treatment—trial brace for immature patients with curves 30–45 degrees and surgery for those >45 degrees (permanent internal fixation rods)

DISORDERS OF THE UPPER LIMB

Nursemaid Elbow

- When longitudinal traction causes radial head subluxation
- **History of sudden traction or pulling on arm**
- Physical exam reveals a child who refuses to bend the arm at the elbow and holds the arm with adduction, internal rotation, and pronation
- Treatment—rotate hand and forearm to the supinated position with pressure of the radial head → reduction

OSTEOMYELITIS AND SEPTIC ARTHRITIS

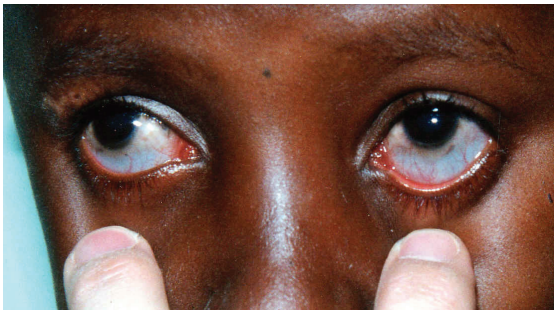
- Etiology
  - **Osteomyelitis:**
    - *S. aureus* most common overall, in all
    - *Pseudomonas*—puncture wound
    - *Salmonella* common in sickle anemia; *S. aureus* still most common
  - **Septic arthritis:**
    - Almost all *S. aureus*
    - Most in young children; hematogenous; LE > UE and other parts of body
- Presentation
  - Pain with movement in infants
  - Older—fever, pain, edema, erythema, warmth, limp, or refusal to walk (acute, toxic, high fever)
- Diagnosis
  - Blood culture, CBC, ESR
  - Radiographic studies:
    - **Initial plain film** if diagnosis not obvious to exclude other causes—trauma, foreign body, tumor; trabecular long bones do not show changes for 7–14 days (septic arthritis shows widening of joint capsule and soft-tissue edema)
    - **Ultrasound for septic arthritis**—joint effusion, guide localization of drainage
    - **Best test is MRI for osteo**; very sensitive and specific
    - Bone scan—can be valuable to augment MRI, especially if multiple foci are suspected or vertebrate
  - Definitive—aspirate for culture and sensitivity
    - Osteomyelitis → bone biopsy for culture and sensitivity
    - Septic arthritis → ultrasound guided arthrocentesis for culture and sensitivity
- Treatment
  - Intravenous antibiotics—always cover for *Staphylococcus* initially (treatment for osteo much longer)

Note

X-rays for patients with **osteomyelitis** are initially normal. Changes are not seen until 10–14 days.

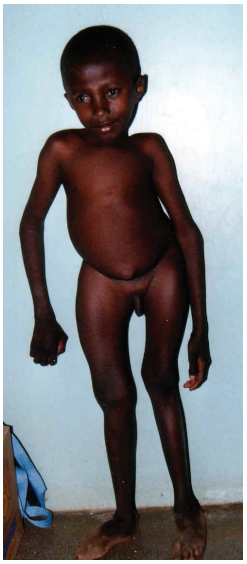
OSTEOGENESIS IMPERFECTA

- Susceptibility to fracture of long bones or vertebral compression from mild trauma
- **Most common genetic cause of osteoporosis;** all types caused by structural or quantitative defects in type I collagen
- **Autosomal dominant**
- **Clinical triad is fragile bones, blue sclera, and early deafness** (and short stature)
- Four types, from perinatally **lethal** to mild, nonlethal
- Diagnosis
  - May see fractures on prenatal ultrasound as early as 6 weeks
  - Rule out child abuse due to fracture and injury history.
  - Confirmed by collagen biochemical studies using fibroblasts cultured from a skin-punch biopsy
- Treatment—no cure; physical rehabilitation; fracture management and correction of deformities



Courtesy of Tom D. Thacher, MD

Figure 17-3. Blue Sclera in Osteogenesis Imperfecta



Courtesy of Tom D. Thacher, MD

Figure 17-4. Skeletal Malformation Due to Osteogenesis Imperfecta

BONE TUMORS

Table 17-1. Comparison of Osteogenic Sarcoma, Ewing Sarcoma, and Osteoid Osteoma

	Osteogenic Sarcoma	Ewing Sarcoma	Osteoid Osteoma
Presentation	Second decade	Second decade	Second decade
M:F	Slightly greater in males	Slightly greater in males	3x greater in males
Predisposition	Retinoblastoma, radiation	None	Male gender
X-ray	Sclerotic destruction: **"sunburst"**	Lytic with laminar periosteal elevation: **"onion skin"**	Small round **central lucency** with sclerotic margin
Malignant	Yes	Yes	No
Metastases	Lungs, bone	Lungs, bone	N/A
Treatment	Chemotherapy, ablative surgery	Radiation and/or surgery	NSAIDs Surgery recommended when associated pain
Prognosis	70% cure without metastasis at diagnosis	60% cure without metastasis at diagnosis	Over time it may resolve spontaneously
Outcome if metastasis	≤20%	20–30%	N/A

Clinical Recall

An adolescent boy with a history of retinoblastoma status post-enucleation of the right eye presents with right shin pain. Right tibia-fibula radiographs are most likely to show which of the following?

A. Lytic lesion with onion skin pattern of periosteal elevation

B. Small round central lucency with sclerotic margin

C. Expansile lucent lesion with endosteal scalloping

D. Sunburst pattern of sclerotic destruction

E. Small sclerotic focus without periosteal reaction

Answer: D

Rheumatic and Vasculitic Disorders 18

Learning Objective

- ❑ Diagnose and describe management of juvenile idiopathic arthritis, systemic lupus erythematosus, Kawasaki disease, and Henoch-Schonlein purpura

JUVENILE IDIOPATHIC ARTHRITIS (JIA)

A 7-year-old girl complains of pain and swelling of the left wrist and right knee off and on for the past 3 months. She has been previously healthy. The pain is worse in the morning and improves throughout the day. Physical examination is remarkable for swelling and effusion of the right knee, with decreased range of motion.

- Definition—idiopathic synovitis of peripheral joints associated with soft-tissue swelling and joint effusion
- Pathophysiology
  - Vascular endothelial hyperplasia and progressive erosion of articular cartilage and contiguous bone
  - Immunogenetic susceptibility and an external trigger
  - **DR8** and **DR5**
- Clinical presentation
  - **Morning stiffness**; easy fatigability
  - Joint pain later in the day, joint swelling, joints warm with decreased motion, and pain on motion, **but no redness**
- Criteria for diagnosis: the diagnosis of JIA is a clinical one, and one of exclusion. There are many diseases that mimic it and there are no pathognomonic diagnostic labs. The clinical exclusion of other diseases is essential, as lab studies may be normal.
  - Age of onset: <16 years
  - Arthritis in 1 or more joints
  - Duration: ≥6 weeks
  - Onset type by disease presentation in first 6 months
  - Exclusion of other forms of arthritis, other connective tissue diseases and vasculitides, **Lyme disease**, psoriatic arthritis, inflammatory bowel disease, **lymphoproliferative disease**

Note

A positive rheumatoid factor in JIA is indicative of a poor prognostic outcome.

- Prognosis for severe and persistent disease
  - Young age at onset
  - RF+
  - Rheumatoid nodules
  - Persistence of anti-cyclic citrullinated peptide (CCP) antibodies (like RF, a marker for more severe disease)
  - Large number of affected joints
  - Involvement of hip, hands and wrists
  - Systemic onset JIA is the most difficult to control in terms of both articular inflammation and systemic manifestations (poorer with polyarthritis, fever >3 months and increased inflammatory markers for >6 months)
- Category of disease:
  - **Pauciarticular (oligoarthritis)**
    - **Pattern**: <5 joints affected in first 6 months; primarily knees (++) and ankles (+), less so the fingers; never presents with hip involvement
    - **Peak age** <6 years
    - **F:M** = 4:1
    - **% of all**: 50–60%
    - **Extra-articular**: 30% with anterior uveitis
    - **Labs**: ANA+ in 60%; other tests normal; may have mildly increased ESR, CRP
    - **Treatment**: NSAIDs + intraarticular steroids as needed; methotrexate occasionally needed
  - **Polyarticular, RF negative**
    - **Pattern**: ≥5 joints in first 6 months; both UE and LE small and large joints; may have C-spine and TMJ involvement
    - **Peak age**: 6–7 years
    - **F:M**: 3:1
    - **% of all**: 30%
    - **Extra-articular**: 10% with anterior uveitis
    - **Labs**: ANA+ in 40%; RF negative; ESR increased (may be significantly), but CRP increased slightly or normal; mild anemia
    - **Treatment**: NSAIDs + methotrexate; if not responsive, anti-TNF or other biologicals (as FDA-approved for children)
  - **Polyarticular RF positive**
    - **Pattern**: ≥5 joints as above but will be aggressive symmetric polyarthritis
    - **Peak age**: 9–12 years
    - **F:M**: 9:1
    - **% of all**: <10%
    - **Extra-articular**: rheumatoid nodules in 10% (more aggressive)

    - Labs: RF positive; ESR greatly increased, CRP increased top normal; mild anemia; if anti-CCP antibodies are positive, then significantly worse disease
    - **Treatment**: long-term remission unlikely; early aggressive treatment is warranted
  - **Systemic Onset**
    - **Pattern**: arthritis may affect any number of joints, but course is usually polyarticular, destructive and ultimately affecting hips, C-spine and TMJ
    - **Peak age**: 2–4 years
    - **F:M:** 1:1
    - **% of all**: <10%
    - **Extra-articular**: For initial diagnosis, in addition to arthritis in ≥1 joint, must have with or be preceded by **fever** ≥2 weeks documented to be quotidian (daily, rises to 39˚ then back to 37˚) for at least 3 days of the ≥2-week period plus ≥1 of the following:
      - **Evanescent** (nonfixed, migratory; lasts about 1 hour) erythematous, salmon-colored rash (linear or circular), most over the trunk and proximal extremities
      - Generalized lymph node involvement
      - Hepatomegaly, splenomegaly or both
      - Serositis (pleuritis, pericarditis, peritonitis)
    - **Labs**: anemia, increased WBCs, increased ESR, CRP, increased platelets
    - **Treatment**: less responsive to standard treatment with methotrexate and anti-TNF agents; consider IL-1 receptor antagonists in resistant cases.
    - May have cervical spine involvement
- Labs
  - No best test; nonspecific: increased acute-phase reactants and anemia of chronic disease
  - Increased **antinuclear antibodies (ANA) in 40–85%**, mostly with poly- and pauciarticular disease
  - **Positive rheumatoid factor (RF+)**—typically with onset of disease in an older child with polyarticular disease and development of rheumatoid nodules
- Treatment
  - Most with pauciarticular disease respond to **nonsteroidal anti-inflammatory drugs (NSAIDs)** alone
  - Additional treatment—**methotrexate (safest and most efficacious of second-line agents)**; azathioprine or cyclophosphamide and biologicals
  - Corticosteroids (few indications):
    - Overwhelming inflammation
    - Systemic illness
    - Bridge treatment
  - Ophthalmology follow up; physical therapy (PT)/occupational therapy

Table 18-1. JRA Prognosis

Category	Serology	Major Problems	Outcome
Polyarticular disease	RF+	Older girls; hand and wrist; erosions, nodules, unremitting	Poor
	ANA+	Younger girls	Good
	Seronegative	—	Variable
Pauciarticular disease	ANA+	Younger girls; chronic iridocyclitis	Excellent, (except eyes)
	RF+	Polyarthritis, erosions, unremitting	Poor
	HLA B27	Older males	Good
	Seronegative	—	Good
Systemic	—	Pauciarticular	Good
	—	Polyarticular	Poor

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

A 10-year-old girl presents with fever, fatigue, and joint pains. Physical examination is remarkable for a rash on the cheeks, swelling of the right knee, and pericardial friction rub. Initial laboratory tests reveal anemia and an elevated blood urea nitrogen and creatinine.

Note

A pregnant woman with SLE will transfer IgG autoantibodies (usually anti-Ro) across the placenta at 12 to 16 weeks. This can cause a variety of manifestations, the most important being **congenital heart block**. All are temporary, except for the heart block, which may require permanent pacing.

- Etiology
  - Autoantibodies, especially against nucleic acids including DNA and other nuclear antigens and ribosomes; blood cells and many tissue-specific antigens; immune complex deposition
    - Immune complex deposition in the dermal/epidermal junction is **specific for SLE** (called the lupus band test)
    - **Diffuse proliferative glomerulonephritis** significantly increases risk for severe renal morbidity (pathology varies from minimal mesangial changes to advanced sclerosing nephritis)
- Epidemiology
  - **90% female**
  - Compared with adults, children have **more severe disease and more widespread organ involvement**
  - Highest rate among African-Americans, Hispanics, Asians, Native-Americans and Pacific Islanders
  - Rare age <5 years and only up to 20% present age <16 years, so **usual presentation is mid-to-late adolescence**

- Clinical presentation
  - Most common is a **female with fever, fatigue, rash, hematological abnormalities (anemia of chronic disease or hemolytic; thrombocytopenia, leukopenia) and arthralgia/arthritis**
  - Renal disease is often asymptomatic, so needs careful monitoring of UA and BP; presents as either flares with quiescent periods or a more smoldering disease (hypertension, glomerulonephritis, nephrosis, acute renal failure)
  - Neuropsychiatric complications can occur with or without active disease
  - Less common: lymphadenopathy, HSM/hepatitis, abdominal pain, diarrhea, melena
- Lab studies
  - **Nonspecific:** elevated ESR, CRP, platelets, anemia, elevated WBC or leukopenia/lymphopenia; decreased CH_{50}, C3, C4 (typically decreased in active disease and increases with treatment)
  - **+ANA**: present in 95–99% of SLE patients but has poor specificity; does not reflect disease activity; first screening test
  - **+anti-dsDNA**: more specific (but not 100%) and correlates with disease activity, especially nephritis
  - **+anti-Smith antibody (anti-Sm):** 100% specific but no disease activity correlation
  - **Antiribonucleoprotein antibodies**: increased with Raynaud phenomenon (blanching of fingers) and pulmonary hypertension; high titer may be diagnostic of mixed CT disorder; antiribosomal-P-antibody is a marker for lupus cerebritis
  - **Anti-Ro antibody (anti-SSA):** IgG maternal antibodies crossing the placenta and produce transient neonatal lupus; may suggest Sjögren syndrome
  - **Anti-La (anti-SSB):** also increased risk of neonatal lupus; may be associated with cutaneous and pulmonary manifestations of SLE or isolated discoid lupus; also seen in Sjögren syndrome
  - **Antiphospholipid antibodies** (APL; including anticardiolipin): when a clotting event occurs in the presence of APL antibodies, the antiphospholipid syndrome is suspected:
    - Increased risk of arterial and venous thrombosis
    - Livedo reticularis
    - Raynaud phenomenon produces cyanosis and then erythema; caused by cold stress or emotional stress; initial arterial vasoconstriction creates hypoperfusion then venous stasis, followed by reflex vasodilation
    - Positive lupus anticoagulant: may give a false-positive serological test for syphilis; also seen in patients with neurological complications
    - Recurrent fetal loss
  - Coombs positive: hemolytic anemia
  - Antiplatelet antibodies: thrombocytopenia
  - Antithyroid antibodies: autoimmune thyroiditis
  - Antihistone antibodies: may be found with **drug-induced lupus**; may act as a trigger in those prone to lupus or cause a reversible syndrome hepatitis is common (otherwise rare in children with lupus); more common drugs: minocycline, tetracycline, sulfasalazine, penicillin, nitrofurantoin, IH, many antihypertensives, anticonvulsants, procainamide, lithium, glyburide, statins, PTU, penicillamine, chlorpromazine, some biologicals

Note

Diagnosis of SLE—"MD Soap 'n Hair"

- **M**alar rash
- **D**iscoid rash
- **S**erositis
- **O**ral ulcers
- **A**NA-positive
- **P**hotosensitivity
- **N**eurologic disorders
- **H**ematologic disorders
- **A**rthritis
- **I**mmune disorders (**LE [lupus erythematosus] prep test**, anti-DNA, Smith)
- **R**enal disorders

- General principles of treatment
  - Sunscreen and direct sun avoidance
  - Hydroxychloroquine for all, if tolerated
  - NSAIDs for joints
  - Corticosteroids for more severe disease, especially renal
  - Steroid-sparing immunosuppressives for severe disease (proliferative GN, continued vasculitis, pulmonary hemorrhage, severe persistent CNS disease)
  - LMW heparin is drug of choice for thrombosis, APL, lupus anticoagulant

Clinical Recall

When considering a diagnosis of systemic lupus erythematosus (SLE), which antibody test would provide both high specificity and correlate with disease activity?

A. ANA

B. Anti-RNP

C. Anti-dsDNA

D. Anti-Smith

E. Antihistone

Answer: C

NEONATAL LUPUS

- Passive transfer of IgG across placenta; most is maternal **anti-Ro and anti-La**
- Mostly presents at age 6 weeks with annular or macular rash affecting the face, especially periorbital area, trunk and scalp after exposure to any UV light; generally lasts 3–4 months
- At risk for future pregnancies; baby is at some risk for future autoantibody disease
- May manifest with any SLE finding, but all resolve unless there is **congenital heart block (can be detected in utero at 16 weeks); is permanent; if it is third degree, pacing is usually required.**

Note

The most serious sequelae of Kawasaki disease are cardiac-related.

KAWASAKI DISEASE

An 18-month-old has had fever for 10 days. He now has conjunctival injection, a very red tongue and cracked lips, edema of the hands, and a truncal rash.

- **Etiology**
  - Many factors point to an infective cause but no specific organism has been found
  - Genetic susceptibility: highest in **Asians** irrespective of location and in children and sibs of those with KD

  - KD-associated antigen in cytoplasmic inclusion bodies of ciliated bronchial epithelial cells, consistent with viral protein aggregates; suggests respiratory portal of entry
  - Seems to require an environmental trigger
- **Epidemiology**
  - Asians and Pacific Islanders at highest risk
  - 80% present at age **<5 years** (median is 2.5 years) but may occur in adolescence
  - Poor outcome predictors with respect to coronary artery disease: very young age, male, neutrophilia, decreased platelets, increased liver enzymes, decreased albumin, hyponatremia, increased CRP, prolonged fever
- **Pathology**
  - **Medium size vasculitis, especially coronary arteries**
  - Loss of structural integrity weakens the vessel wall and results in ectasia or saccular or fusiform aneurysms; thrombi may decrease flow with time and can become progressively fibrotic, leading to stenosis
- **Diagnosis**

  Absolute requirement: fever ≥5 days (≥38.3 C [≥101 F]), unremitting and unresponsive; would last 1–2 weeks without treatment **plus any 4 of the following**:
  - **Eyes:** bilateral bulbar conjunctivitis, non-exudative
  - **Oral:** diffuse oral and pharyngeal erythema, strawberry tongue, cracked lips
  - **Extremities:** edema and erythema of palms and soles, hands and feet acutely; subacute (may have periungual desquamation of fingers and toes and may progress to entire hand)
  - **Rash:** polymorphic exanthema (maculopapular, erythema multiforme or scarlatiniform with accentuation in the groin); perineal desquamation common in acute phase
  - **Cervical lymphadenopathy:** usually unilateral and >1.5 cm, nonsuppurative

Associated symptoms: GI (vomiting, diarrhea, pain); respiratory (interstitial infiltrates, effusions); significant irritability (likely secondary to aseptic meningitis); liver (mild hepatitis, hydrops of gallbladder); GU (sterile pyuria, urethritis, meatitis); joints (arthralgias/arthritis—small or large joints and may persist for several weeks)

- **Cardiac findings**
  - **Coronary aneurysms**: up to 25% without treatment in week 2–3; approximately 2–4% with early diagnosis and treatment; giant aneurysms (>8 mm) pose greatest threat for rupture, thrombosis, stenosis and MI; best detected by 2D echocardiogram
  - **Myocarditis**: in most in the acute phase; tachycardia out of proportion to the fever and decreased LV systolic function; occasional cardiogenic shock; pericarditis with small effusions. About 25% with mitral regurgitation, mild and improves over time; best detected by 2D echocardiogram plus EKG
  - Other arteries may have aneurysms (local pulsating mass)

Note

Any child suspected of having Kawasaki disease should have an echocardiogram.

Note

Kawasaki disease is one of the few instances in pediatrics for which you would use aspirin. (It is usually avoided because of the risk of developing Reye syndrome.)

- **Clinical phases**
  - **Acute febrile:** 1–2 weeks (or longer without treatment), diagnostic and associated findings and lab abnormalities; WBC increased (granulocytes), normocytic /normochromic anemia, normal platelets in first 1–2 weeks; ESR and CRP must be increased (usually significantly for the ESR); sterile pyuria, mild increase in liver enzymes and bilirubin; mild CNS pleocytosis. **Most important tests at admission** are **platelet count, ESR, EKG, and baseline 2D-echocardiogram.**
  - **Subacute:** next 2 weeks; acute symptoms resolving or resolved; extremity desquamation, significant increase in platelet count beyond upper limits of normal (rapid increase in weeks 2–3, often greater than a million); coronary aneurysm, if present, this is the time of highest risk of sudden death. **Follow platelets, ESR and obtain 2nd echocardiogram**.
  - **Convalescent:** next 2–4 weeks; when all clinical signs of disease have disappeared and continue until ESR normalizes; **follow platelet, ESR and if no evidence of aneurysm, obtain 3rd echocardiogram;** repeat echo and lipids at 1 year. If abnormalities were seen with previous echo, more frequent studies are needed, and cardiology follow-up and echocardiograms are tailored to their individual status.
- **Treatment**
  - **Acute:** (at admission): **(a)** IVIG over 10–12 hours (mechanism unknown but results in rapid defervescence and resolution of clinical symptoms in 85–90%); the IVIG gives the large drop in incidence of aneurysms. If continued fever after 36 hours, then increased risk of aneurysm; give 2nd infusion**. (b**) oral high dose aspirin (anti-inflammatory dosing) until afebrile 48 hours
    - If winter, give heat-killed **influenza vaccine** if not yet received (**Reye syndrome**); cannot give varicella vaccine acutely (live, attenuated vaccine and concurrent IVIG would decrease its effectiveness, so must delay any MMR and varicella vaccine until 11 months post-IVIG.
  - **Subacute (convalescent)**: change ASA to low dose (minimum dose for antithrombotic effects as a single daily dose until ESR has normalized at 6–8 weeks and then discontinue if echocardiogram is normal; if abnormalities, continue indefinitely
- **Complications and prognosis**
  - Small solitary aneurysms: continue ASA indefinitely; giant or numerous aneurysms need individualized therapy, including thrombolytic
  - Long-term follow-up with aneurysms: periodic echo and stress test and perhaps angiography; if giant, catheter intervention and percutaneous transluminal coronary artery ablation, direct atherectomy and stent placement (and even bypass surgery)
  - Overall- 50% of aneurysms regress over 1–2 years but continue to have vessel wall anomalies; giant aneurysms are unlikely to resolve
  - Vast majority have normal health
  - Acute KD recurs in 1–3%
  - Fatality rate <1%; all should maintain a heart-healthy diet with adequate exercise, no tobacco and should have intermittent lipid checks.

HENOCH-SCHÖNLEIN PURPURA (HSP)

A 5-year-old boy is seen with maculopapular lesions on the legs and buttocks. He complains of abdominal pain. He has recently recovered from a viral upper respiratory infection. Complete blood cell count, coagulation studies, and electrolytes are normal. Microscopic hematuria is present on urine analysis.

- **Most common vasculitis among children in United States**; leukocytoclastic vasculitis (vascular damage from nuclear debris of infiltrating neutrophils) + **IgA deposition** in small vessels (arterioles and venules) of **skin, joints, GI tract and kidney**.
- Worldwide distribution, all ethnic groups; slightly greater in males; almost all age 3–10 years; occurs mostly in fall, winter and spring, many after a URI
- Infectious trigger is suspected, mediated by IgA and IgA-immune complexes
- Genetic component suggested by occasional family clusters
- Skin biopsy shows vasculitis of dermal capillaries and postcapillary venules with infiltrates of neutrophils and monocytes; in all tissues, immunofluorescence shows IgA deposition in walls of small vessels and smaller amounts of C3, fibrin and IgM
- Clinical presentation:
  - Nonspecific constitutional findings
  - Rash: **palpable purpura**, start as pink macules and then become petechial and then purpuric or ecchymotic; usually symmetric and in gravity-dependent areas (legs and back of arms) and pressure points (buttocks); lesions evolve in crops over 3–10 days and may recur up to 4 months. Usually there is some amount of subcutaneous edema
  - **Arthralgia/arthritis**: oligoarticular, self-limited and in lower extremities; resolves in about 2 weeks, but may recur
  - **GI: in up to 80%:** pain, vomiting, diarrhea, ileus, melena, **intussusception**, mesenteric ischemia or perforation (purpura in GI tract)
  - **Renal: up to 50%:** hematuria, proteinuria, hypertension, nephritis, nephrosis, acute or chronic renal failure
  - Neurological: due to hypertension or CNS vasculitis, possible intracranial hemorrhage, seizures, headaches and behavioral changes
  - Less common: orchitis, carditis, inflammatory eye disease, testicular torsion and pulmonary hemorrhage
- American College of Rheumatology diagnosis: need **2 of the following**:
  (a) palpable purpura
  (b) age of onset <10 years
  (c) bowel angina = postprandial pain, bloody diarrhea
  (d) biopsy showing intramural granulocytes in small arterioles and venules
- **Labs (none are diagnostic)**: increased WBCs, platelets, mild anemia, increased ESR, CRP; stool + for occult blood; increased serum IgA. Must assess and follow BP, UA, serum Cr; GI ultrasound: bowel wall edema, rarely intussusception; skin and renal biopsies would be diagnostic but are rarely performed (only for severe or questionable cases)

- Treatment: supportive and **corticosteroids (with significant GI involvement or life-threatening complications only), although steroids will not alter course/overall prognosis or prevent renal disease**. For chronic renal disease – azathioprine, cyclophosphamide, mycophenolate mofetil.
- Outcome: Most significant **acute complications** affecting morbidity and mortality = serious GI involvement; renal complications are **major long-term** and can develop up to 6 months after initial diagnosis, but rarely if initial UA and BP are normal. Monitor all patients for 6months with BP and UA. Overall prognosis is excellent; most have an acute, self-limited disease; about 30% have >1 recurrence, especially in 4–6 months, but with each relapse symptoms are less. If more severe at presentation, higher risk for relapses; 1–2% with chronic renal disease and 8% ESRD.

Clinical Recall

A 5-year-old boy admitted to the hospital with Henoch-Schonlein purpura develops abdominal pain and a palpable abdominal mass. What is the likely diagnosis?

A. Pyloric stenosis

B. Neuroblastoma

C. Wilms tumor

D. Intussusception

E. Malrotation with volvulus

Answer: D

Hematology 19

Learning Objectives

- ❑ Categorize anemias into those caused by inadequate production, acquired production, and congenital anemias
- ❑ Describe the pathophysiology, diagnosis, and treatment of megaloblastic and hemolytic anemias
- ❑ Recognize and describe management of thalassemias and hemoglobin disorders
- ❑ Demonstrate understanding of coagulation disorders

ANEMIAS OF INADEQUATE PRODUCTION

Physiologic Anemia of Infancy

- Intrauterine hypoxia stimulates erythropoietin → ↑ RBCs (Hb, Hct)
- High F_iO_2 at birth downregulates erythropoietin
- **Progressive drop in Hb over first 2–3 months** until tissue oxygen needs are greater than delivery (typically 8–12 weeks in term infants, to Hb of 9–11 g/dL)
- **Exaggerated in preterm** infants and earlier; nadir at 3–6 weeks to Hb of 7–9 g/dL
- In term infants—no problems, **no treatment;** preterm infants usually need transfusions depending on degree of illness and gestational age

Iron-Deficiency Anemia

An 18-month-old child of Mediterranean origin presents to the physician for routine well-child care. The mother states that the child is a "picky" eater and prefers milk to solids. In fact, the mother states that the patient, who still drinks from a bottle, consumes 64 ounces of cow milk per day. The child appears pale. Hemoglobin is 6.5 g/dL and hematocrit 20%. Mean corpuscular volume is 65 fL.

- Contributing factors/pathophysiology
  - Higher bioavailability of iron in breast milk versus cow milk or formula
  - **Introducing iron-rich foods is effective in prevention.**

  - Infants with decreased dietary iron typically are **anemic at 9–24 months** of age: caused by consumption of large amounts of **cow milk** and foods not enriched with iron; also creates abnormalities in mucosa of GI tract → **leakage of blood**, further decrease in absorption
  - **Adolescents** also susceptible → high requirements during growth spurt, dietary deficiencies, menstruation
- Clinical appearances—**pallor most common;** also irritability, lethargy, pagophagia, tachycardia, systolic murmurs; long-term with neurodevelopmental effects
- Laboratory findings
  - First decrease in bone marrow hemosiderin (iron tissue stores)
  - Then decrease in serum ferritin
  - Decrease in serum iron and transferrin saturation → increased total iron-binding capacity (TIBC)
  - Increased free erythrocyte protoporphyrin (FEP)
  - Microcytosis, hypochromia, poikilocytosis
  - Decreased MCV, mean corpuscular hemoglobin (MCH), increase RDW, nucleated RBCs, low reticulocytes
  - Bone marrow—no stainable iron
- Treatment
  - **Oral ferrous salts**
  - Limit milk, increase dietary iron
  - Within 72–96 hours—peripheral reticulocytosis and increase in Hb over 4–30 days
  - Continue iron for 8 weeks after blood values normalize; repletion of iron in 1–3 months after start of treatment

Note

Pica increases the risk of lead poisoning, iron deficiency, and parasitic infections.

Lead Poisoning

- Blood lead level (BLL) **up to 5 μg/dL** is acceptable.
- Increased risks
  - Preschool age
  - Low socioeconomic status
  - **Older housing (before 1960)**
  - Urban dwellers
  - African American
  - Recent immigration from countries that use leaded gas and paint
- Clinical presentation
  - **Behavioral changes** (most common: hyperactivity in younger, aggression in older)
  - **Cognitive/developmental dysfunction**, especially long-term (also impaired growth)
  - **Gastrointestinal**—anorexia, pain, vomiting, **constipation** (starting at 20 μg/dL)
  - Central nervous system—**related to increased cerebral edema, intracranial pressure (ICP** [headache, change in mentation, lethargy, seizure, coma → death])
  - Gingival lead lines

- Diagnosis
  - Screening—targeted blood lead testing at **12 and 24 months** in high-risk
  - Confirmatory **venous sample—gold standard blood lead level**
  - Indirect assessments—**x-rays of long bones (dense lead lines);** radiopaque flecks in intestinal tract (recent ingestion)
  - Microcytic, hypochromic anemia
  - Increased FEP
  - Basophilic stippling of RBC
- **Treatment: chelation**

Table 19-1. Treatment for Lead Poisoning

Lead Level (µg/dL)	Management
5–14	Evaluate source, provide education, repeat blood lead level in 3 months
15–19	Same *plus* health department referral, repeat BLL in 2 months
20–44	Same *plus* repeat blood lead level in 1 month
45–70	Same *plus* chelation: single drug, preferably dimercaptosuccinic acid (succimer, oral)
≥70	Immediate hospitalization *plus* 2-drug IV treatment: ethylenediaminetetraacetic acid (EDTA) plus British anti-lewisite (BAL)

CONGENITAL ANEMIAS

Congenital Pure Red-Cell Anemia (Blackfan-Diamond)

A 2-week-old on routine physical examination is noted to have pallor. The birth history was uncomplicated. The patient has been doing well according to the mother.

- **Increased RBC programmed cell death → profound anemia by 2–6 months**
- **Congenital anomalies**
  - **Short stature**
  - Craniofacial deformities
  - Defects of upper extremities; **triphalangeal thumbs**
- Labs
  - Macrocytosis
  - Increased HbF
  - **Increased RBC adenosine deaminase (ADA)**
  - **Very low reticulocyte count**
  - Increased serum iron
  - **Marrow with significant decrease in RBC precursors**

- Treatment
  - **Corticosteroids**
  - **Transfusions and deferoxamine**
  - If hypersplenism, splenectomy; mean survival 40 years without stem cell transplant
- Definitive—**stem cell transplant** from related histocompatible donor

Congenital Pancytopenia

Note

Blackfan-Diamond

Triphalangeal thumbs

Pure RBC deficiency

Fanconi

Absent/hypoplastic thumbs

All cell lines depressed

A 2-year-old presents to the physician with aplastic anemia. The patient has microcephaly, microphthalmia, and absent radii and thumbs.

- Most common is **Fanconi anemia**—spontaneous chromosomal breaks
- Age of onset from infancy to adult
- Physical abnormalities
  - Hyperpigmentation and café-au-lait spots
  - **Absent or hypoplastic thumbs**
  - **Short stature**
  - Many other organ defects
- Labs
  - Decreased RBCs, WBCs, and platelets
  - Increased HbF
  - **Bone-marrow hypoplasia**
- Diagnosis—bone-marrow aspiration and cytogenetic studies for chromosome breaks
- Complications—increased risk of **leukemia (AML) and other cancers**, organ complications, and bone-marrow failure consequences (infection, bleeding, severe anemia)
- Treatment
  - **Corticosteroids and androgens**
  - **Bone marrow transplant definitive**

Clinical Recall

Which lab finding differentiates Diamond-Blackfan anemia from congenital pancytopenia?

A. Decreased red blood cells (RBCs)

B. Increased RBC adenosine deaminase

C. Increased HbF

D. Low reticulocytes

E. Low white blood cells and platelets

Answer: B

ACQUIRED ANEMIAS

Transient Erythroblastopenia of Childhood

- **Transient hypoplastic anemia between 6 months–3 years**
  - Transient **immune suppression** of erythropoiesis
  - Often after nonspecific viral infection (not parvovirus B19)
- Labs—decreased reticulocytes and bone-marrow precursors, normal MCV and HbF
- Recovery generally **within 1–2 months**
- Medication not helpful; may need 1 transfusion if symptomatic

Anemia of Chronic Disease and Renal Disease

- Mild decrease in RBC lifespan and relative failure of bone marrow to respond adequately
- Little or no increase in erythropoietin
- Labs
  - Hb typically 6–9 g/dL, **most normochromic and normocytic (but may be mildly microcytic and hypochromic)**
  - Reticulocytes normal or slightly decreased for degree of anemia
  - Iron low without increase in TIBC
  - Ferritin may be normal or slightly increased.
  - Marrow with normal cells and normal to decreased RBC precursors
- Treatment—control underlying problem, may need erythropoietin; rarely need transfusions

MEGALOBLASTIC ANEMIAS

Background

- RBCs at every stage are larger than normal; there is an asynchrony between nuclear and cytoplasmic maturation.
- **Ineffective erythropoiesis**
- Almost all are **folate or vitamin B12 deficiency** from malnutrition; uncommon in United States in children; more likely to be seen in adult medicine.
- Macrocytosis; nucleated RBCs; **large, hypersegmented neutrophils**; low serum folate; iron and vitamin B12 normal to decreased; marked increase in lactate dehydrogenase; hypercellular bone marrow with megaloblastic changes

Folic Acid Deficiency

- Sources of folic acid—green vegetables, fruits, animal organs
- Peaks at 4–7 months of age—irritability, failure to thrive, chronic diarrhea
- Cause—inadequate intake (pregnancy, **goat milk feeding,** growth in infancy, chronic hemolysis), decreased absorption or congenital defects of folate metabolism
- Differentiating feature—low serum folate
- Treatment—daily folate; transfuse only if severe and symptomatic

Note

Hypersegmented neutrophils have >5 lobes in a peripheral smear.

Note

If autoimmune pernicious anemia is suspected, remember the Schilling test and antiparietal cell antibodies.

Vitamin B12 (Cobalamin) Deficiency

- Only animal sources; produced by microorganisms (humans cannot synthesize)
- Sufficient stores in older children and adults for 3–5 years; but in **infants born to mothers with deficiency, will see signs in first 4–5 months**
- Inadequate production (extreme restriction [**vegans**]), lack of intrinsic factor (congenital pernicious anemia [rare], autosomal recessive; also juvenile pernicious anemia [rare] or gastric surgery), impaired absorption (terminal ileum disease/removal)
- Clinical—weakness, fatigue, failure to thrive, irritability, pallor, **glossitis**, diarrhea, vomiting, jaundice, many **neurologic symptoms**
- Labs—normal serum folate and decreased vitamin B12
- Treatment—parenteral B12

Table 19-2. Comparison of Folic Acid Versus Vitamin B12 Deficiencies

	Folic Acid Deficiency	Vitamin B12 (Cobalamin) Deficiency
Food sources	Green vegetables, fruits, animals	Only from animals, produced by microorganisms
Presentation	Peaks at 4–7 months	Older children and adults with sufficient stores for 3–5 years Infants born to mothers: first signs 4–6 months
Causes	Goat milk feeding Chronic hemolysis Decreased absorption Congenital defects of folate metabolism	Inadequate production (vegans) Congenital or juvenile pernicious anemia (autosomal recessive, rare) Gastric surgery Terminal ileum disease
Findings	Low serum folate with normal to increased iron and vitamin B12	Normal serum folate and decreased vitamin B12
Treatment	Daily folate	Parenteral vitamin B12

HEMOLYTIC ANEMIAS

Hereditary Spherocytosis and Elliptocytosis

- Most **autosomal dominant**
- Abnormal shape of RBC due to **spectrin deficiency → decreased deformability → early removal of cells by spleen**
- Clinical presentation
  - **Anemia and hyperbilirubinemia in newborn**
  - **Hypersplenism, biliary gallstones**
  - Susceptible to aplastic crisis (parvovirus B19)

- Labs
  - Increased reticulocytes
  - Increased bilirubin
  - Hb 6–10 mg/dL
  - Normal MCV; **increased mean cell Hb concentration (MCHC)**
  - **Smear—spherocytes or elliptocytes diagnostic**
- Diagnosis
  - Blood smear, family history, increased spleen size
  - Confirmation—**osmotic fragility test**
- Treatment—transfusions, splenectomy (after 5–6 years), folate

Enzyme Defects

Pyruvate kinase (glycolytic enzyme)

- Wide range of presentation
  - Some degree of pallor, jaundice, and splenomegaly
  - Increased reticulocytes, mild macrocytosis, polychromatophilia
- Diagnosis—**pyruvate kinase (PK) assay** (decreased activity)
- Treatment—exchange transfusion for significant jaundice in neonate; transfusions (rarely needed), splenectomy

Glucose-6-phosphate dehydrogenase (G6PD)

A 2-year-old boy presents to the physician's office for an ear check. Three weeks earlier, the child had an ear infection that was treated with trimethoprim-sulfamethoxazole. On physical examination the patient is noted to be extremely pale. Hemoglobin and hematocrit are 7 g/dL and 22%, respectively.

- Two syndromes
  - **Episodic hemolytic anemia** (most common)
  - Chronic nonspherocytic hemolytic anemia
- **X-linked;** a number of abnormal alleles
- Episodic common among **Mediterranean, Middle Eastern, African, and Asian** ethnic groups; wide range of expression varies among ethnic groups
- Within 24–48 hours after ingestion of an **oxidant (acetylsalicylic acid, sulfa drugs, antimalarials, fava beans) or infection and severe illness** → rapid drop in Hb, hemoglobinuria and jaundice (if severe)
- Acute drop in Hb, saturated haptoglobin → free Hb and hemoglobinuria, **Heinz bodies**, increased reticulocytes
- Diagnosis—**direct measurement of G6PD activity**
- Treatment—prevention (avoid oxidants); supportive for anemia

HEMOGLOBIN DISORDERS

Sickle Cell Anemia (Homozygous Sickle Cell or S-Beta Thalassemia)

A 6-month-old, African-American infant presents to the pediatrician with painful swollen hands and swollen feet.

- Occurs in endemic malarial areas: sub-Saharan Africa, Middle East, India; survival advantage with heterozygous trait provides protection against falciparum infection
  - Hydrophobic valine residues → HbS polymerizes in the deoxygenated state, decreased pH; increased [HbS] in RBCs → characteristic sickle RBC shape (reversible)
  - With repeated episodes → irreversible RBC sickling → become stiff and nondeformable → vasooclusion → tissue ischemia and intra- and extravascular hemolysis.
- Single base pair change (thymine for adenine) at sixth codon of the beta gene (valine instead of glutamic acid)
  - Sickle cell disease: up to 65% are SS, but there are also compound heterozygotes with Hg SC the most common, then HbSβ0 and then HbSβ+
  - Hgb S-beta thal – 0 (α2β2s, α2β2Th-0): clinically same as Hb SS
  - Hgb S –beta thal + (α2β2s, α2β2Th-+): variable depending on specific β-thalassemia mutation
  - Hgb SC (α2β2s, α2β2c): same as Hb SS but less frequent events
- Sickle cell trait (Hb AS)
  - Life span normal; serious complications rare
  - CBC normal; normal RBC life span
  - No limitation of activities
  - Known complications: **hematuria, renal papillary necrosis, hyposthenuria**; splenic infarction at **high altitude** (>3000 m); exertional rhabdomyolysis, sudden death
- Clinical presentation
  - Effects on blood: after transition to adult beta globin expression in 4–6 months; with health, maintains stable Hb at 6–9 g/dL; significant fluctuations occur with disease complications; also, typical leukocytosis (15–25,000) and mild thrombocytosis (400–475,000)
  - Newborn usually without symptoms; development of hemolytic anemia over **first 2–4 months (replacement of HbF)**; as early as age 6 months; some children have **functional asplenia; by age 5, all have functional asplenia**
  - First presentation usually **hand-foot syndrome (acute distal dactylitis)**—symmetric, painful swelling of hands and feet (ischemic necrosis of small bones)
  - **Infection:** S. *pneumonia* with functional asplenia; peak in first 3 years of life; penicillin prophylaxis (orally 2x/day or monthly benzathine penicillin IM age 2 months –5 years) decreases rate by 84% and *S. pneumoniae* vaccine by another 70%
  - **Acute painful crises (vaso-occlusive):**
    - Severe, episodic pain
    - Increased with age and peak age 20s
    - Bone marrow ischemia, leading to possible infarction

- Triggers: infection, emotional stress, cold, wind, high altitude, dehydration
- **Younger:** mostly fingers and toes (acute distal dactylitis in infant beginning age 5–7 months), arms and legs; **with increasing age**: lower back, head, chest, abdomen

– More extensive **vaso-occlusive crises** → ischemic damage
- Skin ulcers
- Retinopathy
- Avascular necrosis of hip and shoulder
- Infarction of bone and marrow (increased risk of ***Salmonella*** **osteomyelitis**)
- **Splenic autoinfarction**
- Pulmonary: **acute chest syndrome** (along with sepsis, most common causes of mortality)
  - New pulmonary infiltrate on chest x-ray with ≥1 of the following: fever, tachypnea, dyspnea, hypoxia, chest pain
  - 45% with no identifiable cause
  - 30% infection: most recent statistics now show *C. pneumoniae* and *M. pneumoniae* are most common causes of acute chest syndrome in children; then viruses, and then *S. pneumoniae*
  - Also caused by pulmonary infarction and fat embolism
  - Treatment: oxygen, antibiotics, bronchodilators, analgesia, fluids, transfusion as needed; consider exchange transfusion if severe and progressive
- **Stroke (peak age 6–9 yrs):** most are ischemic of middle cerebral artery; treatment is rapid reduction in percent SS with RBC transfusion or partial automated exchange transfusion; resolution or marked decrease in 24–48 hrs; second stroke more likely without use of regular RBC transfusion program to suppress percent of SS (chronic transfusion regiment); best long-term treatment is stem cell transplant; current routine screening with annual transcranial Doppler study to detect cerebral blood flow velocity related to risk of stroke
- **Priapism**, especially in adolescence

– **Acute splenic sequestration:** rapid spleen enlargement, decreased [Hb], and decreased platelets; 30% by age 5 yrs (most age <2); teach family splenic palpation (early detection decreases mortality; remove spleen preventively if occurs again)

– **Aplastic crisis**: after infection with **parvovirus B19**; absence of reticulocytes during acute anemia; maturational arrest of RBC precursors in marrow for 10-14 days; because in SS disease, RBC lifespan is only 10-20 days instead of normal 120, there is profound anemia; need transfusional support until reticulocytes return; may hasten recovery with IVIG

– Cholelithiasis: symptomatic gallstones; sudden hemolysis → increased serum bilirubin → stores in gall bladder and can precipitate to form stones

• Labs

– Increased reticulocytes

– Mild to moderate anemia

– Normal MCV

– If severe anemia: smear for **target cells,** poikilocytes, hypochromasia, **sickle RBCs,** nucleated RBCs, **Howell-Jolly bodies** (lack of splenic function); bone marrow **markedly hyperplastic**

- Renal: glomerular and tubular dysfunction; hyposthenuria in all; also gross hematuria, nephrotic syndrome, renal infarction, pyelonephritis, papillary necrosis, and end-stage renal disease requiring dialysis/transplant

- Diagnosis
  - Every state with mandatory newborn screening program; identify newborns with the disease for prompt referral to providers with expertise and initiation of penicillin before age 4 months
  - Most commonly used procedures are thin layer/isoelectric focusing and high-performance liquid chromatography
  - Those with abnormal screens are retested at first clinical visit (and after age 6 months) to determine final hemoglobin phenotype; also a CBC and Hb phenotype determination is recommended for both parents to confirm the diagnosis and provide an opportunity for genetic counseling
- Treatment—prevent complications
  - Immunize (pneumococcal regular *plus* **23-valent**, meningococcal)
  - **Penicillin prophylaxis** at 2 months until age 5
  - Educate family (assessing illness, palpating spleen, etc.)
  - Folate supplementation
  - Aggressive antibiotic treatment of infections
  - Pain control
  - **Transfusions** as needed
  - Monitor for risk of stroke with **transcranial Doppler**
  - **Hydroxyurea**: only FDA-approved drug for sickle cell disease; inhibits polymerization in frequent painful crises by increasing expression of fetal Hb
  - **Stem-cell transplant**: only curative option; reserved for those with severe and life-threatening complications

Note

Patients without a functioning spleen are predisposed to infection with encapsulated organisms. Pneumococcal vaccines 13 (PCV13) and 23 (PPSV23) are necessary.

Clinical Recall

Which of the following infectious complications of sickle cell disease is correctly matched to its causative organism?

A. Osteomyelitis: *Streptococcus*

B. Pneumonia: *Pseudomonas*

C. Dactylitis: *Coxsackie virus*

D. Acute chest syndrome: *Staphylococcus*

E. Aplastic crisis: Parvovirus B19

Answer: E

THALASSEMIAS

Alpha Thalassemia

- The genes for alpha chains are duplicated: there are 2 pairs of alleles (4 genes) on chromosome 16. Mutations are caused by complete gene deletions, so there are 4 syndromes.
  - **Alpha thalassemia silent trait**
    - Common in African Americans
    - One gene deletion; clinically silent
    - Diagnosis requires molecular analysis: no abnormal hemoglobins, no increase in HbF (in contrast to beta thalassemias)
- **HgB H disease**: deletion of 3 genes; Hgb Barts >25% in newborn period and easily diagnosed with electrophoresis
  - At least 1 parent has alpha-thalassemia trait; later beta-tetramers develop (Hgb H—interact with RBC membrane to produce Heinz bodies) and can be identified electrophoretically; microcytosis and hypochromia with mild to moderate anemia; target cells present, mild splenomegaly, jaundice and cholelithiasis
  - Typically do not require transfusions or splenectomy; common in Southeast Asians
- Alpha-thalassemia major: deletion of 4 genes; severe fetal anemia resulting in hydrops fetalis
  - Newborn has predominantly Hgb Barts with small amounts of other fetal Hgb; immediate exchange transfusions are required for any possibility of survival; transfusion-dependent with only chance of cure (bone marrow transplant)

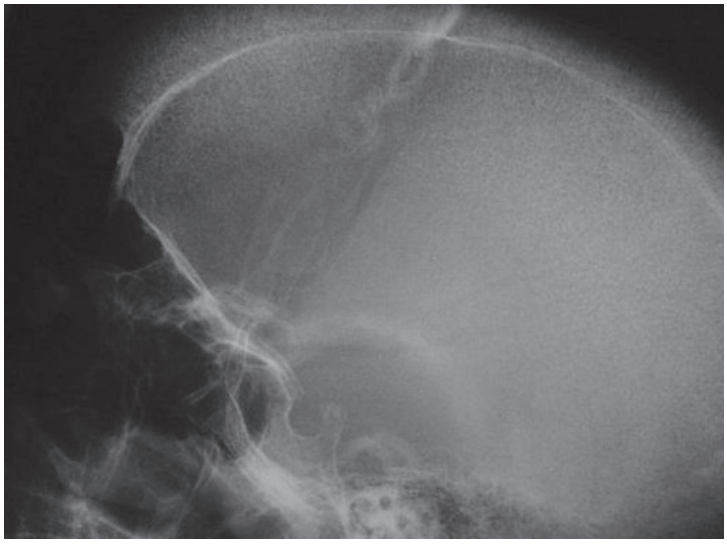


Figure 19-1. Skull X-ray Demonstrating "Hair on End" Appearance of Thalassemia

Beta Thalassemia Major (Cooley Anemia)

A 9-year-old has a greenish-brown complexion, maxillary hyperplasia, splenomegaly, and gallstones. Her Hb level is 5 g/dL and MCV is 65 mL.

- Mutations in the beta gene result from point mutations (>200 known mutations), which are collected into the following clinical groupings: beta thalassemia trait, minima, minor, intermedia, and major (no beta chains, Cooley anemia).
- **Excess alpha globin chains → alpha tetramers** form; **increase in HbF** (no problem with gamma-chain production)
- Presents in second month of life with progressive **anemia, hypersplenism, and cardiac decompensation** (Hb <4 mg/dL)
- **Expanded medullary space** with increased expansion of **face and skull (hair-on-end)**; extramedullary hematopoiesis, **hepatosplenomegaly**
- Labs
  - Infants born **with HbF only** (seen on **Hgb electrophoresis**)
  - **Severe anemia**, low reticulocytes, increased nucleated RBCs, hyperbilirubinemia microcytosis
  - **No normal cells seen on smear**
  - **Bone-marrow hyperplasia; iron accumulates → increased serum ferritin and transferrin saturation**
- Treatment
  - Transfusions
  - **Deferoxamine** (assess iron overload with liver biopsy)
  - May need splenectomy
  - **Bone-marrow transplant** curative

HEMORRHAGIC DISORDERS

Evaluation of Bleeding Disorders

Note

Minor bleeds = von Willebrand

Deep bleeds = hemophilia

History provides the most useful information for bleeding disorders.

- **von Willebrand disease (vWD) or platelet dysfunction → mucous membrane bleeding, petechiae, small ecchymoses**
- **Clotting factors—deep bleeding with more extensive ecchymoses and hematoma**
- Laboratory studies
  - Obtain **platelets**, bleeding time, **PT, PTT**
    - If normal, von Willebrand factor (vWF) testing and thrombin time
    - If abnormal, further clotting factor workup
  - **Bleeding time**—platelet function and interaction with vessel walls; **qualitative platelet defects or vWD** (platelet function analyzer)
  - Platelet count—thrombocytopenia is the most common acquired cause of bleeding disorders in children
  - PTT—**intrinsic pathway:** from initiation of clotting at level of factor XII through the final clot (prolonged with factor VIII, IX, XI, XII deficiency)

- PT—measures **extrinsic pathway** after activation of clotting by thromboplastin in the presence of Ca^{2+}; **prolonged by deficiency of factors VII, XIII or anticoagulants**; standardized values using the **International Normalized Ratio (INR)**
- Thrombin time—measures the **final step: fibrinogen → fibrin**; if prolonged: **decreased fibrin or abnormal fibrin** or substances that interfere with fibrin polymerization (**heparin or fibrin split products**)
- Mixing studies: if there is a prolongation of PT, PTT, or thrombin time, then add normal plasma to the patient's and repeat labs
  - **Correction of lab prolongation suggests deficiency of clotting factor.**
  - **If not or only partially corrected, then it is due to an inhibitor (most common on inpatient basis is heparin).**
  - **If it becomes more prolonged with clinical bleeding, there is an antibody directed against a clotting factor (mostly factors VIII, IX, or XI).**
  - **If there is no clinical bleeding but both the PTT and mixing study are prolonged, consider lupus anticoagulant (predisposition to excessive clotting).**
- Clotting factor assays—each can be measured; severe deficiency of factors VIII or IX = <1% of normal; moderate = 1–5%; mild = >5%
- Platelet aggregation studies—if suspect a **qualitative platelet dysfunction, ristocetin**

Table 19-3. Clinical Findings in Coagulopathies

	Factor VIII	Factor IX	vWF
Platelet	Normal	Normal	Normal
PT	Normal	Normal	Normal
PTT	↑	↑	↑
Bleeding time	Normal	Normal	↑
Factor VIII	↓	Normal	Normal
Factor IX	Normal	↓	Normal
vWF	Normal	Normal	↓
Sex	Male	Male	Male/female
Treatment	Factor VIII, desmopressin	Factor IX	Fresh frozen plasma, cryotherapy, DDAVP

Hemophilia A (VIII) and B (IX)

- 85% are A and 15% B; no racial or ethnic predisposition
- **X-linked**
- Clot formation is delayed and not robust → **slowing of rate of clot formation**
  - With crawling and walking—**easy bruising**
  - Hallmark is **hemarthroses**—earliest in ankles; in older child, knees and elbows
  - Large-volume blood loss into iliopsoas muscle (inability to extend hip)—vague groin pain and hypovolemic shock
  - Vital structure bleeding—life-threatening

Note

There is no way to clinically differentiate factors VIII and IX deficiencies. You must get specific factor levels.

- Labs
  - 2× to 3× **increase in PTT** (all others normal)
  - **Correction with mixing studies**
  - Specific assay confirms:
    - Ratio of VIII:vWF sometimes used to diagnose carrier state
    - Normal platelets, PT, bleeding time, and vW Factor
- Treatment
  - Replace specific factor
  - **Prophylaxis now recommended** for young children with severe bleeding (intravenous via a central line every 2–3 days); prevents chronic joint disease
  - For mild bleed—patient's endogenous factor can be released with **desmopressin** (may use intranasal form)
  - Avoid antiplatelet and aspirin medications
  - DDAVP increases factor VIII levels in mild disease

von Willebrand Disease (vWD)

- Most common hereditary bleeding disorder; **autosomal dominant**, but more females affected
- Normal situation—vWF adheres to subendothelial matrix, and platelets then adhere to this and become activated; also **serves as carrier protein for factor VIII**
- Clinical presentation—**mucocutaneous bleeding** (excessive bruising, epistaxis, menorrhagia, postoperative bleeding)
- Labs—**increased bleeding time and PTT**
- **Quantitative assay for vWFAg, vWF activity** (ristocetin cofactor activity), plasma factor VIII, determination of vWF structure and platelet count
- Treatment—need to increase the level of vWF and factor VIII
  - Most with type 1 DDAVP **induces release of vWF**
  - For types 2 or 3 need replacement → **plasma-derived vWF-containing concentrates with factor VIII**

Other Bleeding Disorders

Vitamin K deficiency

- **Newborn needs intramuscular administration of vitamin K or develops bleeding diathesis**
- Postnatal deficiency—lack of oral intake, alteration in gut flora (long-term antibiotic use), malabsorption
- Vitamin K is fat soluble so deficiency associated with a decrease in factors **II, VII, IX, and X and proteins C and S**
- Increased PT and PTT with normal platelet count and bleeding time

Liver disease

- **All clotting factors produced exclusively in the liver, except for factor VIII**
- Decreases proportional to extent of hepatocellular damage
- Treatment—**fresh frozen plasma** (supplies all clotting factors) and/or **cryoprecipitate** (supplies fibrinogen)

PLATELET DISORDERS

Immune Thrombocytopenic Purpura (ITP)

A 4-year-old child previously healthy presents with petechiae, purpura, and excessive bleeding after falling from his bicycle.

- **Autoantibodies** against platelet surface
- Clinical presentation
  - Typically 1–4 weeks after a nonspecific **viral infection**
  - Most 1–4 years of age → **sudden onset of petechiae and purpura with or without mucous membrane bleeding**
  - Most resolve within 6 months
  - **<1% with intracranial hemorrhage**
  - 10–20% develop chronic ITP
- Labs
  - **Platelets <20,000/mm^3**
  - **Platelet size normal to increased**
  - **Other cell lines normal**
  - **Bone marrow—normal to increased megakaryocytes**
- Treatment
  - **Transfusion contraindicated** unless life-threatening bleeding (platelet antibodies will bind to transfused platelets as well)
  - No specific treatment if platelets >20,000 and no ongoing bleeding
  - If very low platelets, ongoing bleeding that is difficult to stop or life-threatening:
  - **Intravenous immunoglobulin for** 1–2 days
    - If inadequate response, then prednisone
  - Splenectomy reserved for older child with severe disease

Note

With ITP, the physical examination is otherwise normal; **hepatosplenomegaly and lymphadenopathy should suggest another disease**.

Oncology 20

Learning Objectives

- ❑ Categorize and describe management of leukemia and lymphomas
- ❑ Describe the epidemiology and management of brain tumors and other malignancies

LEUKEMIA AND LYMPHOMA

Acute Lymphoblastic Leukemia

A 5-year-old patient is seen due to a limp. On physical examination a low-grade fever, URI symptoms, hepatosplenomegaly, and petechiae are seen.

- Predisposing conditions (majority): trisomy 21, Fanconi anemia, ataxia-telangiectasia, Wiskott-Aldrich syndrome, neurofibromatosis, Blackfan-Diamond syndrome
- Other predisposing factors: siblings (2–4 x increase; greater for twins), radiation, certain chemotherapeutic agents, B-cell ALL with EBC (Burkitt)
- The first disseminated cancer shown to be curable
- Striking peak incidence at age 2–3 years and greater in boys; most by age 15
- 85% from progenitor B-cells
- 77% of all childhood leukemias (AML 11%, CML 2–3%, juvenile myelomonocytic 1–2%; others rare and chronic)
- Presentation: initially nonspecific
  - **Bone** (often severe) and **joint pain** (often with swelling and effusion)
  - Then signs and symptoms of **bone marrow failure**: RBCs (pallor, anorexia, exercise intolerance); platelets (bruising, bleeding); WBCs (fever, either from disease itself or infection)
  - Then **organ infiltration**: lymphadenopathy; splenomegaly (less so hepatomegaly); testicular swelling/pain; ± CNS (headache, increased ICP, neuropathies, seizures)
- Diagnosis
  - Best initial step (after H and P) is **CBC, differential, platelets, and smear;** almost all have **anemia and thrombocytopenia** (WBCs <10,000 and blasts may be reported as **atypical lymphocytes**); with high WBCs, possible lymphoblasts

Note

ALL is both CALLA (common acute lymphoblastic leukemia antigen) and TdT-positive.

  - Then, immediate **bone marrow aspirate** (>25% homogeneous population of lymphoblasts) and **staging lumbar puncture** (thus staging at diagnosis is from bone marrow aspirate + lumbar puncture)
  - WBC mostly <10,000/mm^3 (atypical lymphocytes); poor prognosis if >100,000
  - **Best test is bone marrow aspirate → lymphoblasts**
  - If chromosomal abnormalities, poor prognosis
- Treatment
  - Remission induction (bone marrow leukemic cell eradication + intrathecal)
  - CNS therapy reduces relapse rate to <10%
  - Consolidation and intensification
  - Maintenance 2–3 years
- Complications
  - Majority is **bone marrow relapse** (15–20%):
    - **Increased intracranial pressure (ICP) or isolated cranial nerve palsies**
    - **Testicular relapse** in 1–2% of boys
  - ***Pneumocystis* pneumonia**
  - Other infections because of immunosuppression
  - **Tumor lysis syndrome**—result of initial chemotherapy (cell lysis): hyperuricemia, hyperkalemia, hyperphosphatemia → hypocalcemia (tetany, arrhythmias, renal calcinosis)
    - Treat with hydration and alkalinization of urine; prevent uric acid formation (allopurinol)
- Prognosis: >85% 5-year survival

BRAIN TUMORS

Brain tumors are the second most common tumors in children and have the highest mortality, especially <5 years old. In order of incidence, these are: infratentorial tumors, supratentorial tumors, spinal cord tumors, and tumors of multiple sites.

The predominant type varies with age:

- First year—supratentorial; most common: **choroid plexus tumors and teratomas**
- Age 1–10—infratentorial; most are **juvenile pilocytic astrocytomas** (usually cerebellar; low-grade, rarely invasive) and tumors of the **medulloblastoma, ependymoma, and brainstem**
- Age >10 years—supratentorial; most common: **diffuse astrocytoma** (also glioblastoma multiforme)
  - **Craniopharyngioma:** histologically benign, slow-growing tumor that predominantly involves the sella and suprasellar space; **presenting complaints:** headaches, visual symptoms, behavioral changes, growth failure, delayed puberty, amenorrhea, diabetes insipidus, panhypopituitarism; no role for chemotherapy—treated with surgery and radiation

  - **Optic nerve glioma:** most frequent optic nerve tumor; benign, slowly progressive; increased incidence in neurofibromatosis; possible symptoms: unilateral visual loss, proptosis, eye deviation, optic atrophy, strabismus, nystagmus; treatment is observation unless symptomatic (chiasm involvement = radiation/chemotherapy, proptosis and visual loss = surgery)

More common in children than adults are tumors of the **optic path, hypothalamus, brainstem, and pineal-midbrain.**

The clinical presentation of pediatric brain tumors depends on location, type, and age, and symptoms may present as secondary to **CSF obstruction** (increased ICP, focal brain dysfunction). Common signs and symptoms:

- **Supratentorial**—subtle changes in personality, mentation, and speech; focal deficits; neuroendocrine if near third ventricle
- **Midline or infratentorial**—headache, nausea, vomiting, papilledema, blurred vision, diplopia; disturbances in equilibrium, gait, and coordination
- **Brainstem**—gaze palsy, cranial nerve palsies, upper motor neuron defects, motor weakness

When brain tumor is suspected, perform CT scan (**best initial test**) followed by MNRI (overall best test). Treatment is specific to the tumor's type and invasiveness.

OTHER MALIGNANCIES

Wilms Tumor

A mother brings her 3-year-old child to the physician because she found an abdominal mass while bathing the child. The child has been in her usual state of health according to the mother. However, on review of the vital signs, the patient is noted to have an elevated blood pressure.

- **Nephroblastoma** (Wilms tumor)
- **Second most common malignant abdominal tumor**
  - Usual age 2–5 years
  - One or both kidneys (bilateral in 7%)
  - **Associations:**
    - **Hemihypertrophy**
    - **Aniridia**
    - **Genitourinary anomalies**
    - **WAGR**
- Clinical presentation—most are **asymptomatic abdominal mass**; can have symptoms if encroaching on other organs: hypertension (increased renin), abdominal pain, bowel obstruction (rectal), hematuria
- Diagnosis
  - Best initial test–ultrasound
  - **Abdominal CT scan confirmatory test**

- Treatment
  - Surgery
  - Then chemotherapy and radiation
  - Bilateral renal—unilateral nephrectomy and partial contralateral nephrectomy
- Prognosis—54 to 97% have 4-year survival

Neuroblastoma

A 2-year-old child is brought to the physician because of bluish skin nodules, periorbital proptosis, and periorbital ecchymosis that have developed over the last few days. On physical examination, a hard smooth abdominal mass is palpated.

Note

Patients with neuroblastoma can present with ataxia or opsomyoclonus ("dancing eyes and dancing feet"). These patients may also have Horner syndrome.

- **From neural crest cells, due to N-myc oncogene; can occur at any site**
- 8% of childhood malignancies
- Most are
  - Adrenal
  - Retroperitoneal sympathetic ganglia
  - Cervical, thoracic, or pelvic ganglia
- Firm, palpable mass in flank or midline; **painful; with calcification and hemorrhage**
- Initial presentation often as **metastasis**—long bones and **skull, orbital**, bone marrow, lymph nodes, liver, skin
- Diagnosis
  - Plain x-ray, CT scan, MRI (overall best)
  - Elevated urine **homovanillic acid (HVA)** and **vanillylmandelic acid (VMA)** in 95% of cases
  - Evaluate for spread—bone scan, bone marrow (neuroblasts) → staging from I (organ of origin) to IV (disseminated)
- Treatment
  - Surgery
  - Chemotherapy and radiation
  - Stem cell transplant (definitive)

Pheochromocytoma

Note

Children with pheochromocytoma excrete predominantly norepinephrine-increased VMA and metanephrine. Children with neuroblastoma usually do not have hypertension, and major metabolites are dopamine and HVA.

- **Catecholamine-secreting** tumor from chromaffin cells
- **Most common site—adrenal medulla,** but can occur anywhere along abdominal sympathetic chain
- Children age 6–14 years; 20% are bilateral, and some with multiple tumors
- Autosomal dominant; associated with **neurofibromatosis,** *MEN-2A* and *MEN2B*, tuberous sclerosis, Sturge-Weber syndrome, and ataxia-telangiectasia
- Clinical presentation
  - **Episodic severe hypertension**, palpitations and diaphoresis, headache, abdominal pain, dizziness, pallor, vomiting, sweating, encephalopathy
  - Retinal examination—**papilledema, hemorrhages, exudate**
- Labs—significant increase in blood or **urinary levels of catecholamines and, metabolites**

- Diagnosis
  - Significant increase in blood/urinary VMA and metanephrine
  - CT scan (best initial test), then MRI
  - Some adrenal masses are difficult to localize; scan with I-131 metaiodobenzylguanidine (MBIG), which is taken up by chromaffin tissue
- Treatment—**surgical removal** (high-risk) **with preoperative alpha and beta blockade** and IV fluids

Rhabdomyosarcoma

A mother brings her 3-year-old daughter to the physician for evaluation because the young girl has "grapes" growing out of her vagina.

- Most common soft-tissue malignancy in children
- Almost any site, which determines presentation; determination of specific histologic type needed for assessment and prognosis. Most are in the head and neck.
- Increased frequency in **neurofibromatosis**
- Types
  - **Embryonal**—60%
    - Intermediate prognosis
  - **Botryoid** (projects; grapelike)—**vagina**, uterus, bladder, nasopharynx, middle ear
  - Alveolar—15%
    - Very poor prognosis
    - Trunk and extremities
  - Pleomorphic—adult form; very rare in children
- Clinical presentation
  - Mass that may or may not be painful
  - Displacement or destruction of normal tissue
  - Easily disseminates to lung and bone
- Diagnosis—depends on site of presentation
  - Biopsy, CT, MRI, U/S, bone scan
- Treatment—best prognosis with completely resected tumors (but most are not completely resectable)
  - Chemotherapy pre- and postoperatively; radiation

Clinical Recall

A 7-year-old girl with an abdominal mass diagnosed by MIBG imaging is found to have elevated urinary catecholamines. With which systemic disease is this mass associated?

A. MEN 1

B. von Hippel-Lindau

C. Tuberous sclerosis

D. WAGR

E. Basal cell nevus syndrome

Answer: C

Neurology 21

Learning Objectives

- ❑ Describe the epidemiology and treatment of febrile and other seizure disorders
- ❑ Describe CNS anomalies, neurocutaneous syndromes, and neurodegenerative disorders
- ❑ Recognize and categorize encephalopathies
- ❑ Categorize and describe the epidemiology and genetics of neuromuscular disease

CENTRAL NERVOUS SYSTEM (CNS) ANOMALIES

Neural Tube Defects

Elevated **alpha-fetoprotein** is a marker for neural tube defects.

Spina bifida occulta

- Midline defect of vertebral bodies **without protrusion** of neural tissue; occasionally associated with other anomalies
- Most **asymptomatic and of no clinical consequence**
- May have **overlying midline lumbosacral defect** (patch of hair, lipoma, dermal sinus)

Tethered cord

- **Ropelike filum terminale persists and anchors the conus below L2**
- Abnormal tension—asymmetric lower extremity growth, deformities, bladder dysfunction, progressive scoliosis, diffuse pain, **motor delay**
- Most associated with a **midline skin lesion**
- **MRI needed for precise anatomy**
- Surgical transection

Meningocele

- Meninges herniate through defect in posterior vertebral arches
- **Fluctuant midline mass well covered with skin**; may transilluminate
- Must determine extent of neural involvement with MRI
  - CT scan of head for possible hydrocephalus
  - Surgery

Myelomeningocele

The pediatrician is called to the delivery room because an infant is born with a defect in the lumbosacral area.

- Strong evidence that **maternal periconceptional use of folate** reduces risk by half
- May occur anywhere along the neuraxis, but most are **lumbosacral**
- **Low sacral lesions—bowel and bladder incontinence and perineal anesthesia without motor impairment**

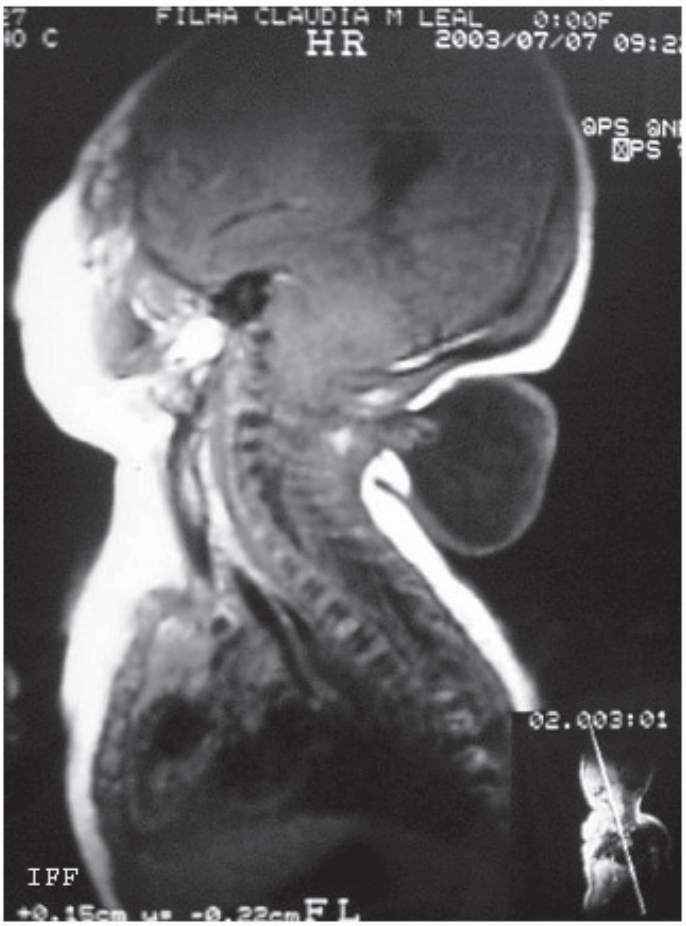


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Figure 21-1. Arnold-Chiari Malformation, a Defect of the Hindbrain Usually Accompanied by Myelomeningocele

- Midlumbar lesion—**saclike cystic structure** covered by thin, partially epithelized tissue
  - **Flaccid paralysis** below the level of the lesion is most common; no deep tendon reflexes (DTRs), no response to touch and pain
  - **Urinary dribbling, relaxed anal sphincter**

Note

Almost every child with a sacral or lower lumbar spine lesion will achieve some form of **functional ambulation**, and half of those with higher spine defects will have some degree of hip flexor and hip adductor movement.

- 80% associated with **hydrocephalus; type II Chiari malformation**—may have symptoms of hindbrain dysfunction (feeding difficulty, choking, stridor, apnea, vocal cord paralysis, upper extremity spasticity)
- Evaluation and treatment
  - Must evaluate for other anomalies prior to surgery
  - Evaluate renal function
  - **Head CT scan for possible hydrocephalus**
  - Treatment—**ventriculoperitoneal shunt and correction of defect**

Hydrocephalus

A 2-month-old infant is noted to have a head circumference >95th percentile.

- Definition—**impaired circulation and absorption of CSF** or, rarely, from increased CSF production from a choroid plexus papilloma
- Types
  - **Obstructive** (noncommunicative) versus **nonobstructive** (communicative) from obliteration of subarachnoid cisterns or malfunction of arachnoid villi
    - Obstructive—most are **abnormalities of the cerebral aqueduct** (stenosis or gliosis; congenital, intrauterine infection, mumps, hemorrhage) **or lesions near the fourth ventricle** (brain tumor, Chiari malformation, Dandy-Walker malformation)
  - Nonobstructive—occurs mostly with **subarachnoid hemorrhage**; also with pneumococcal or TB meningitis or leukemic infiltrates
- Clinical presentation—depends on rate of rise of intracranial pressure
  - Infants:
    - **Increased head circumference**
    - **Bulging anterior fontanel**
    - Distended scalp veins
    - Broad forehead
    - **"Setting sun" sign**
    - Increased DTRs
    - Spasticity, clonus
  - Older child (subtler symptoms)
    - Irritability
    - Lethargy
    - Poor appetite
    - Vomiting
    - **Headache**
    - **Papilledema**
    - **Sixth-nerve palsy**
- **Treatment for all types of hydrocephalus—shunting**

Dandy-Walker malformation

- **Cystic expansion of fourth ventricle due to absence of roof**
- Associated **agenesis of posterior cerebellar vermis** and corpus callosum
- Presents with increasing head size and **prominent occiput**, long-tract signs, **cerebellar ataxia,** and delayed motor development, positive transillumination

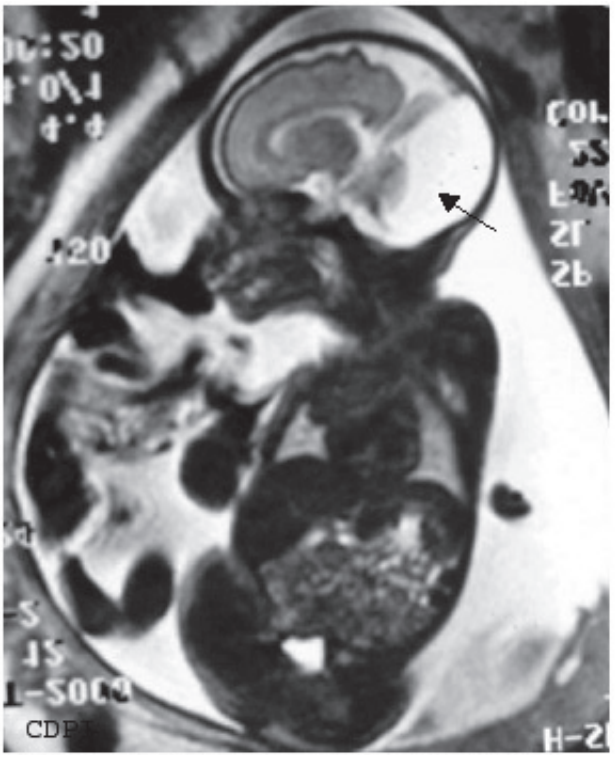

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Figure 21-2. Dandy Walker Malformation, the Result of Agenesis or Hypoplasia of the Cerebellar Vermis, Cystic Dilatation of the Fourth Ventricle, and Enlargement of the Posterior Fossa

SEIZURES

Seizures are triggered recurrently from within the brain versus somatic disorders that may trigger a seizure from outside the brain. **Epilepsy** is present when **at least 2 unprovoked seizures occur >24 hours apart.**

Febrile Seizures

An 18-month-old child is brought to the emergency center after having a generalized tonic-clonic seizure that lasted approximately 5 min. The parents say that the child had been previously well but developed cold symptoms earlier today with a temperature of 39 C (102 F).

- Occurs between age 6 months to 5 years; incidence peaks at age 14–18 months and may reoccur with fever
- Usually positive family history
- Temperature usually increases **rapidly** to >39 C (102 F)
- **Typical: generalized tonic-clonic seizures, <10–15 minutes; brief postictal period**
- **Atypical: >15 minutes, more than 1 in a day, and focal findings**
- Simple febrile seizure has **no increased risk of epilepsy**—risk for febrile seizures is increased with atypical seizure, family history of epilepsy, initial seizure before age 6 months, abnormal development, or preexisting neurologic disorder
  - Workup/Evaluation
    - Must determine cause of fever, must not look like meningitis
    - **No routine labs, no EEG, no neuroimaging**
  - Treatment—**control fever**

Partial Seizures

Simple seizures

- **Asynchronous tonic or clonic movements; most of the face, neck, and extremities;** average duration 10–20 seconds
- Some have **an aura** and may verbalize during the attack; **no postictal period**
- EEG—**spike and sharp waves or multifocal spikes**
- Treatment—phenytoin and other anticonvulsants

Complex seizures

- **Impaired consciousness at some point,** may be very brief; one-third with aura (always indicates focal onset)
- **Automatisms** common after loss of consciousness (lip-smacking, chewing, swallowing, increased salivation)
- Interictal EEG—**anterior temporal lobe shows sharp waves or focal spikes**
- **MRI—many will show abnormalities in temporal lobe** (sclerosis, hamartoma, cyst, infarction, arteriovenous malformation [AVM], glioma)
- Treatment—**carbamazepine (drug of choice)** and other add-ons

Generalized Seizures

Absence (petit mal) seizures

- **Sudden cessation of motor activity or speech with blank stare and flickering eyes**
- **More in girls; uncommon <5 years of age**
- **No aura**; usually <30 seconds; **no postictal period**
- EEG—**3/second spike and generalized wave discharge**
- Treatment—**ethosuximide (drug of choice)**, valproic acid (second line)

Tonic-clonic seizures

- May have **aura (focal onset; may indicate site of pathology)**; loss of consciousness, eyes roll back, tonic contraction, apnea
- **Then clonic rhythmic contractions** alternating with relaxation of all muscle groups
- Tongue-biting, loss of bladder control
- Semicomatose for up to 2 hours afterward with vomiting and bilateral frontal headache
- Treatment—**valproic acid, phenobarbital, phenytoin, carbamazepine**, and other add-ons

Myoclonic Seizures

- Repetitive seizures—**brief, symmetric muscle contraction** and loss of body tone with falling forward
- Five types, with variable severity, morbidity, and prognosis
- **Treatment—valproic acid** and others

Infantile Spasms

- **Symmetric contractions of neck, trunk, and extremities** (with extension episodes as well)
- Pathophysiology—increased corticotropin-releasing hormone (CRH): neuronal hyperexcitability
- Begin typically at 4–8 months of age
- Types
  - **Cryptogenic**—infant is normal prior to seizure with normal neurologic examination and development; **good prognosis**
  - **Symptomatic**—disease present prior to seizure (e.g., tuberous sclerosis); **poor control and intellectual disability**
- EEG—**hypsarrhythmia** (asynchronous, chaotic bilateral spike-and-wave pattern)
- Treatment
  - **Adrenocorticotropic hormone (ACTH); drug of choice**
  - **Prednisone** and add-on of other anticonvulsants if no response

Neonatal Seizures

  - Because of immaturity of CNS, **tend to have subtle seizures**; therefore, they are difficult to recognize
- Etiology
  - **Hypoxic ischemic encephalopathy most common; seizure usually present within 12–24 hours after birth**
  - CNS **infection**
  - CNS **hemorrhage**
  - **Structural** abnormalities
  - Blood chemistry abnormalities
  - **Inborn errors** of metabolism
  - **Drug withdrawal**

Note

Benign Myoclonus of Infancy

- Often confused with myoclonic seizures
- Clusters confined to the neck, trunk, and extremities
- EEG normal
- Good prognosis
- Goes away after 2 years; no treatment

- Evaluation:
  - CBC; platelets
  - Electrolytes, calcium, magnesium, phosphorus; glucose
  - Lumbar puncture to exclude meningitis or bleed
  - CT scan in term, ultrasound in preterm to diagnose bleed
  - Blood and urine culture may be indicated (+CSF)
  - Consider newborn screen for inborn errors of metabolism, if abnormal results suggestive or no diagnosis
  - Treatment—lorazepam, phenobarbital

Table 21-1. Neonatal Seizures

Cause	Presentation	Associations
Hypoxic ischemic encephalopathy	12–24 hours	Term; cerebral palsy
Intraventricular hemorrhage	1–7 days	Preterm
Metabolic	Variable	IODM (infant of diabetic mother), inborn errors of metabolism, DiGeorge syndrome
Infection	Variable	TORCH, maternal fever, sepsis/meningitis

Clinical Recall

A 2-year-old boy with fever, rhinorrhea, and cough is seen in the emergency department after having a first-time generalized tonic-clonic seizure which lasted 6-7 minutes. The exam is notable for a tired-appearing child with no focal neurologic signs or nuchal rigidity. There is no lethargy or irritability. There is no sensitivity to light and no mental status changes or vomiting. What is the next step?

A. Lumbar puncture

B. EEG

C. Brain MRI

D. Prescribe acetaminophen

E. Prescribe ethosuximide

Answer: D

NEUROCUTANEOUS SYNDROMES

A 6-year-old presents to the pediatrician for a routine evaluation. The child is noted to have 10 café-au-lait lesions as well as axillary freckling.

Neurofibromatosis (NF; von Recklinghausen Disease)

NF-1

- **Autosomal dominant**; but most with new mutation
- Every organ can be affected; features **present from birth but complications may be delayed into adulthood**
- Diagnosis—a good history and physical examination are needed to make the diagnosis.
  - **Two** of the following are needed:
    - At least 5 café-au-lait spots >5 mm prepubertal or at least 6 café-au-lait spots >15 mm postpubertal
    - Axillary/inguinal freckling
    - >2 iris Lisch nodules (seen on slit lamp only)
    - >2 neurofibromas or 1 plexiform neurofibroma
    - Osseous lesions, sphenoid dysplasia or cortical thinning of long-bones (LE)
    - Optic gliomas
- Complications
  - CNS:
    - Low-grade **gliomas (optic), hamartomas**
    - **Malignant neoplasms** (astrocytoma, neurofibrosarcoma, and others)
    - Transient ischemic attack, hemiparesis, hemorrhage
    - Complex partial or generalized **seizures**
    - **Cognitive defects**, learning disabilities, attention deficit, speech abnormalities, psychiatric disturbances
  - **Renovascular hypertension or pheochromocytoma**
  - Increased incidence **of leukemia, rhabdomyosarcoma, Wilms tumor**
- Treatment
  - Genetic counseling
  - Early detection of treatable conditions
  - Annual ophthalmologic examination
  - Examine family members

NF-2

- Presentation
  - Primary feature—**bilateral acoustic neuromas**
  - Hearing loss
  - Facial weakness
  - Headache
  - Unsteady gait

  - **Skin findings much less common** (glioma, meningioma, schwannoma)
  - CNS tumors common
- Treatment
  - Developmental and cognitive evaluation and diagnosis
  - Prevent pathological fractures if LE cortical thinning present

Tuberous Sclerosis

A 1-month-old infant presents with infantile spasms and has a hypsarrhythmic EEG pattern.

- **Autosomal dominant**; half with new mutations
- Wide range of manifestations within same family
- The younger the patient, the higher the likelihood of intellectual disability
- Hallmark is CNS **tubers** found in **convolutions of cerebral hemispheres**; undergo calcification and project into ventricular cavity, causing obstruction of CSF flow and hydrocephalus.
- Clinical presentation
  - Infancy—with **infantile spasms** and characteristic skin lesions
    - **Ash-leaf macule**—hypopigmented; increased with Wood UV lamp
    - CT scan shows **calcified tubers** (but may not see till 3–4 years of age)
  - Childhood—**generalized seizures and skin lesions**
    - **Sebaceous adenoma**—red or clear nodules on nose and cheeks
    - **Shagreen patch**—rough, raised lesion with orange-peel consistency; most in lumbosacral area (midline)
- Diagnosis—**clinical:** characteristic skin lesions and seizure disorder
- Treatment—seizure control
- Complications
  - Retinal lesions—either mulberry tumor from optic nerve head or phakomas (round, flat, gray lesions in area of disc)–visual disturbances
  - Brain tumors much less common (but may see malignant astrocytoma)
  - Half have **rhabdomyoma of the heart** (can detect in fetus with echocardiogram); most spontaneously regress over first 2 years
  - **Renal lesion in most—either hamartoma or polycystic kidneys**
  - Pulmonary—cystic or fibrous changes

Sturge-Weber (SW) syndrome

A newborn is examined in the nursery by the pediatrician. The patient is a product of a term spontaneous vaginal delivery without complications. On physical examination, the patient is noted to have a facial nevus.

- **Facial nevus (port wine stain), seizures, hemiparesis, intracranial calcifications, and intellectual disability**
- **Nevus is always present at birth and always involves at least the upper face and eyelid**

Note

Not all babies with a facial nevus have Sturge-Weber syndrome. Obtain a skull x-ray and intraocular pressure.

- **Glaucoma** in ipsilateral eye
- Presentation
  - **Seizures in most** (focal tonic-clonic, **contralateral to the nevus**); becomes refractory and slowly develops **hemiparesis, intellectual disability**
- Diagnosis
  - **Skull x-ray shows occipital-parietal calcifications (serpentine or railroad-track appearance) and intraocular pressure reading initially** (↑)
  - **CT scan to highlight extent and show unilateral cortical atrophy and hydrocephalus ex vacuo**
- Treatment
  - Conservative if seizures are well controlled and development is not severely affected
  - Hemispherectomy or lobectomy—may prevent intellectual disability and recalcitrant seizures if done in the first year of life
  - Regular intraocular pressure evaluation
  - Nevus—pulsed laser
  - Special education

ENCEPHALOPATHIES

Cerebral Palsy

- Group of motor syndromes from disorders of early brain development
  - Neurologic function may change or progress with time
  - Some have cognitive dysfunction
  - **Most born at term with uncomplicated labor and delivery**
    - Majority have no identifiable antenatal problems
    - **Only 10% with intrapartum asphyxia**
- **The most obvious manifestation is impaired ability of voluntary muscles (rigidity and spasticity).**
  - Other associations—seizures and abnormalities of speech, vision, and intellect
- Other risk factors—increased risk with intrapartum infection, **low birth weight,** (especially <1,000 g); most of these secondary **to intraventricular hemorrhage and periventricular leukomalacia**
- Diagnosis
  - MRI (location and extent of lesions or abnormalities)
  - If spinal involvement, MRI of spine
  - Hearing and visual evaluation
  - Genetic evaluation
  - Complete neurologic and developmental exams
- Treatment
  - Multidisciplinary team
  - Teach daily activities, exercises, assistance and adaptive equipment, surgical release procedures, communication equipment
  - Spasticity drugs (dantrolene, baclofen, botulinum toxin)
  - Psychological support

NEURODEGENERATIVE DISORDERS

The hallmark of neurodegenerative disorders is typically **progressive deterioration of neurologic function**. This includes loss of speech, vision, hearing, and/or walking; feeding difficulties, cognitive dysfunction, and possible seizures; and regression of developmental milestones.

Friedrich Ataxia

- Abnormal gene encoding for frataxin; autosomal recessive
- Onset of **ataxia** before <10 years of age
  - Slowly progressive
  - Loss of DTRs
  - Extensor plantar reflex
  - Weakness in hands and feet
  - Degeneration of posterior columns—loss of position and vibration sense
- **Explosive, dysarthric speech**
- Skeletal abnormalities, e.g., kyphoscoliosis
- **Hypertrophic cardiomyopathy—refractory congestive heart failure, death**

Wilson Disease

- Inborn error of **copper metabolism**; autosomal recessive
- Liver with or without CNS disease (neurologic, psychiatric)
- Liver symptoms first (any liver pathology), neurologic symptoms later (adolescent to adults)
  - Dystonia, tremors, basal ganglia problems
  - **Kayser-Fleischer rings**—pathognomonic (all will have with neuropsych symptoms)
  - MRI shows dilated ventricles with atrophy of cerebrum and lesions in thalamus and basal ganglia
- Diagnosis—**Suspect in any child with acute or chronic liver disease, unexplained neurologic disease, or behavioral or psychiatric changes**
  - **Best screen**—serum ceruloplasmin (decreased)
  - Confirm with liver biopsy—increased Cu content
  - Screen family members
- Treatment
  - Chelation with **penicillamine** (slows progression)
  - Definitive treatment with liver transplant

Sphingolipidoses

Tay-Sachs disease

- Deficient β-**hexosaminidase-A**, accumulate GM2
- Mostly in Ashkenazi Jews (carrier rate 1 in 30)
- Normal developmental until 6 months, then lag and lose milestones
- Seizures, hypotonia, blindness
- **Cherry-red macula**

Purine Metabolism Disorders

Lesch-Nyhan disease

- X-linked
- Purine metabolism disorder of purine metabolism → excess uric acid
- Delayed motor development after a few months
- **Self-mutilation and dystonia,** gouty arthritis, tophi, renal calculi
- Choreoathetosis, spasticity
- Diagnosis–**Analyze HPRT enzyme**
- Treatment
  - Manage renal complications, arthritis
  - Behavioral modification
  - Medication for reduction of anxiety and mood stabilization

Clinical Recall

Which of the following neurodegenerative disorders is correctly matched to a key finding?

A. Lesch-Nyhan disease: cherry red macula

B. Tay-Sachs disease: deficient hexosaminidase-A

C. Wilson disease: error of iron metabolism

D. Friedrich ataxia: dilated cardiomyopathy

E. Niemann-Pick disease: Kayser-Fleischer rings

Answer: B

NEUROMUSCULAR DISEASE

Spinal Muscle Atrophy (SMA)

A pediatrician examines an infant who is on the examination table in frog-leg position, with subdiaphragmatic retractions and absent tendon reflexes.

- **Degenerative disease of motor units beginning in the fetus and progressing into infancy; denervation of muscle and atrophy**
- Types
  - **SMA 1 = severe infantile (Werdnig-Hoffmann disease)**
  - SMA 2 = late infancy, slower progression
  - SMA 3 = chronic juvenile (Kugelberg-Welander disease)
- Autosomal recessive
- Clinical presentation—SMA 1 presents in early infancy with
  - **Progressive hypotonia; generalized weakness;** Infant is flaccid, has little movement and poor head control
  - **Feeding difficulty**
  - **Respiratory insufficiency**
  - **Fasciculations of the tongue and fingers**
  - **Absent DTRs**
- Typically appear **brighter** than others of same age
- Diagnosis
  - **Simplest, most effective diagnosis is molecular genetic marker in blood for the *SMN* gene.**
  - EMG—fibrillation potential and other signs of denervation
  - Muscle biopsy shows a characteristic pattern of **perinatal denervation.**
- Treatment is supportive; there is no cure; most die in first 2 years of life

Myasthenia Gravis

A pediatrician examines an infant with poor sucking and swallowing since birth. The infant is noted to be a floppy baby with poor head control. There is associated ocular ptosis and weak muscles on repeated use.

- Immune-mediated neuronal blockade; motor end plate is less responsive due to, decreased number of available **acetylcholine receptors** secondary to **circulating receptor binding antibodies**; generally nonhereditary
- Clinical presentation
  - **Ptosis and extraocular muscle weakness is the earliest and most consistent finding.**
  - Dysphagia and facial weakness, and early infant feeding difficulties
  - Poor head control

Note

Transient Neonatal Myasthenia

- Neonates born to mothers with myasthenia; may have generalized hypotonia and weakness, feeding difficulties, and respiratory insufficiency from days to weeks
- May need ventilation and nasogastric feedings
- After antibodies wane, they are normal and have no risk for disease.

  - Limb-girdle weakness and in distal muscles of hands
  - **Rapid muscle fatigue**, especially late in the day
  - May have respiratory muscle involvement
- Diagnosis
  - **EMG more diagnostic than muscle biopsy**—decremental response to repetitive nerve stimulation, reversed after giving cholinesterase inhibitor (edrophonium) → improvement within seconds
  - CPK is normal.
  - May have anti-acetylcholine (anti-ACh) antibodies (inconsistent)
- Treatment
  - Mild—many need no medication
  - Cholinesterase-inhibiting drugs—either neostigmine bromide PO or pyridostigmine
  - Severe—long-term prednisone; if no response, intravenous immunoglobulin (Ig), then plasmapheresis
  - Thymectomy—most effective if patient has high anti-ACh titers and symptoms for <2 years
- Complications—do not tolerate neuromuscular blockade and aminoglycosides potentiate

Hereditary Motor-Sensory Neuropathies (HMSNs)

HMSN I: Marie-Charcot-Tooth disease

- Progressive disease of peripheral nerves; **peroneal muscle atrophy; peroneal and tibial nerves**
- Autosomal dominant
- Clinical presentation
  - Asymptomatic until late childhood or adolescence but may have problem with gait as early as age 2 years
  - **Clumsy, fall easily; muscles of anterior compartment of lower leg become wasted → stork-like appearance**
  - **Pes cavus, foot drop**
  - **Claw hand** (in worse cases)
  - **Slowly progressive** through life, but normal lifespan and remain ambulatory
- Diagnosis
  - CPK is normal.
  - **Decreased nerve conduction velocities** (motor and sensory)
  - **Sural nerve biopsy** is diagnostic.
  - Blood molecular genetic diagnosis
- Treatment
  - **Stabilize ankles**
  - Surgical ankle fusion
  - Protection from trauma
  - If sensory problems, phenytoin or carbamazepine

Guillain-Barré syndrome

- **Postinfectious polyneuropathy**—mostly motor; all ages; most with demyelinating neuropathy
- 10 days after a **nonspecific viral illness or *Campylobacter jejuni or Mycoplasma pneumoniae*—Landry ascending paralysis**
  - Symmetric proximal and distal muscles
  - Gradually over days to even weeks
  - May have **tenderness, pain, paresthesias early**
  - **Bulbar involvement** in half—dysphagia, facial weakness, **respiratory insufficiency**
  - May have **autonomic involvement**—blood pressure lability, bradycardia, asystole
  - Spontaneous recovery begins in 2–3 weeks; some have residual weakness; improvement in inverse direction
- Diagnosis
  - Significant **increase in CSF protein** with **normal glucose** and **no cells**
  - Reduced motor and sensory nerve conductions
- Treatment
  - Mostly supportive
  - **Admit all patients** (observe respiratory effort)
    - Mild-observation
  - **Intravenous immunoglobulin** 2–5 days
  - May need plasmapheresis, steroids, interferon, or other immunosuppressives

Muscular Dystrophy

Duchenne

A 3-year-old boy is brought to the pediatrician because he is very clumsy. According to his parents, he has difficulty climbing stairs and frequently falls. On physical examination hypertrophy of the calves is noted.

- Primary myopathy with genetic basis; is progressive and results in degeneration and death of muscle fibers; most common of the neuromuscular diseases in all races and ethnic groups; X-linked recessive
- Clinical presentation
  - First sign may be poor head control in infancy.
  - By year 2, may have subtle findings of hip-girdle weakness
  - **Gower sign** as early as age 3 years but fully developed by **age 5–6 years;** with hip-waddle gait and lordotic posturing
  - **Calf pseudohypertrophy** (fat and collagen) and wasting of thigh muscles
  - Most walk without orthotic devices until age 7–10 years, then with devices until 12; once a wheelchair is required, **significant acceleration of scoliosis**

- Progressive into second decade:
  - Respiratory insufficiency
  - Repeated pulmonary infections
  - Pharyngeal weakness (aspiration)
  - Contractures
  - **Scoliosis** (further pulmonary compromise)
  - **Cardiomyopathy** is a constant feature.
  - **Intellectual impairment** in all; IQ <70 in about 30%; most with **learning disabilities**

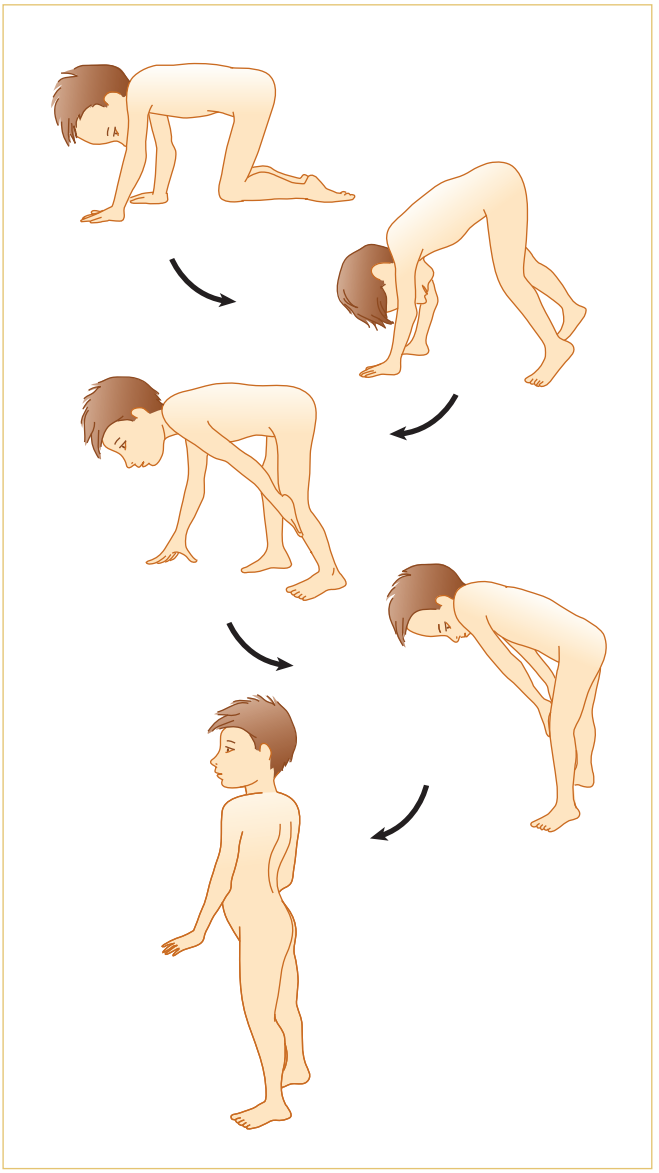

Figure 21-3. Gower Sign in Duchenne Muscular Dystrophy

  - **Death usually around age 18 years** from respiratory failure in sleep, intractable heart failure, pneumonia, aspiration with obstruction
- Lab studies
  - **CPK—15,000–35,000** U/L (normal is <160 U/L) (initial screen for myopathy)
  - **Best initial test—molecular genetic diagnosis: deficiency or defective dystrophin cytoskeletal protein from gene at Xp21.2**
  - **Muscle biopsy** to show the abnormal or absent dystrophin; most accurate test (do if dystrophin-negative)
- Treatment—multidisciplinary team
  - **Digoxin** for heart failure (all patients need cardiology referral)
  - Vigorous treatment of pulmonary infections
  - Maintain good **nutrition**; good calcium supply (prevent osteoporosis)
  - **Physiotherapy**—delay contractions; **orthotic devices**, proper wheelchair, physiatrist

Myotonic Dystrophy

Myotonic dystrophy is the **second most common muscular dystrophy**.

- **Autosomal dominant** inheritance; CTG trinucleotide expansion at 19q13.3; causes multiple dysfunctions in multiple organ systems
- Involves both **striated and smooth muscle**
- Most common findings may be present at birth; the **severe congenital form** occurs in a baby born to a mother with symptomatic disease:
  - **Facial wasting: Inverted V-shaped upper lip, thin cheeks, scalloped concave temporalis muscles, narrow head, high arched palate**
  - **Hypotonia**: mild weakness and progressive wasting of DISTAL muscles especially hands, then dorsal forearm and anterior compartment of lower leg, then atrophy of proximal muscles
  - Progressive difficulty in climbing steps and lastly a Gower sign
  - **Slow progression** through childhood to adulthood but rare to lose ability to walk
  - **NOTE: The distal distribution of muscle wasting is the exception to the general rule of myopathies having a proximal and neuropathies a distal distribution**
  - **Myotonia: not evident until age >5; very slow relaxation of muscle after a contraction, but NOT a painful muscle spasm (difficulty opening fist or relaxing grip)**
- Other problems:
  - Poor speech articulation, slurred
  - Difficulty swallowing, aspiration pneumonia
  - Extraocular muscle weakness; cataracts
  - Slow GI emptying, constipation
  - Ineffective uterine contractions
  - Heart block and arrhythmia (not cardiomyopathy as in other dystrophies)
  - Many endocrine problems
    - Half with intellectual impairment
- Diagnosis: CPK as a screen (in the hundreds compared to MD); EMG classic myotonic findings; best test is DNA (blood); biopsy not needed
- Treatment: supportive

Clinical Recall

Which of the following is true about muscular dystrophy versus myotonic dystrophy?

A. Creatine kinase is only elevated in myotonic dystrophy.

B. Gower sign is only seen in myotonic dystrophy.

C. Calf pseudohypertrophy is only seen in muscular dystrophy.

D. Distal muscle involvement is seen only in muscular dystrophy.

E. Trinucleotide repeats are present only in muscular dystrophy.

Answer: C

Infectious Disease 22

Learning Objectives

- ❑ Describe the presentation and emergency management of meningitis
- ❑ Describe the presentation and management of pertussis
- ❑ Recognize and describe treatment for mycobacteria, Lyme disease, and Rocky Mountain Spotted Fever
- ❑ Categorize and describe other important mycotic, viral, and helminthic diseases

MENINGITIS

A 6-year-old presents to the physician with the chief complaint of headache, vomiting, neck stiffness, and photophobia. Physical examination reveals an ill-appearing child unable to flex his neck without eliciting pain. Kernig and Brudzinski signs are positive.

Acute Bacterial (Older Than a Neonate)

- First 2 months of life (and some into month 3) represent maternal vaginal flora—group B *Streptococcus, E.coli, Listeria*
- Age 2 months to 12 years—***S. pneumoniae*** (peaks in first 2 years), ***N. meningitidis*** (sporadic or in epidemics; direct contact from a daycare center or a colonized adult family member; increased in college freshmen living in dorms), and HiB (now **uncommon** due to many years of immunization)
- Pathology—meningeal inflammation and exudate
  - Most from hematogenous spread, initially from bacterial colonization of nasopharynx, and a prior or current viral infection may enhance pathogenicity
  - Rarely from an infection at a contiguous site (sinusitis, otitis media [OM], mastoiditis, orbital cellulitis)

Note

Infants may not have positive Kernig or Brudzinski sign in meningitis but will have bulging fontanelles on physical examination.

- Clinical presentation
  - Several days of **fever, lethargy, irritability, anorexia, nausea, vomiting**
  - Then **meningeal irritation** (photophobia, neck and back pain, and rigidity)
    - **Kernig sign:** flexing of hip 90° and subsequent pain with leg extension (inconsistent)
    - **Brudzinski sign:** involuntary flexing of knees and hips after passive flexing of the neck while supine (better test)
  - Increased ICP suggested by headache, emesis, bulging anterior fontanelles, **oculomotor or abducens palsies**, hypertension with bradycardia, apnea, decorticate or decerebrate posturing, stupor, coma
- Diagnosis—**need lumbar puncture (LP) and blood culture in all** (90% have positive blood culture)
  - **Contraindications to immediate LP**
    - Evidence of increased ICP
    - Severe cardiopulmonary problems requiring resuscitation
    - Infection of skin over site
    - Do not delay antibiotics for the CT scan.

Table 22-1. CSF Findings in Various Types of Meningitis

	Bacterial	Partially Treated	Granulomatous (TB)	Aseptic (Viral)
Cells/mL	200–5,000	200–5,000	100–500	100–700
Cytology	Polymorphonuclear neutrophil	Mostly polymorphonuclear neutrophil	Lymphocytes	Mostly lymphocytes
Glucose†	Low	Low	Low	Normal
Protein	High	High	High	Normal to slightly high
Gram stain	Positive	Variable	Negative	Negative
Culture	Positive	Variable	Positive	Negative
CIE or LA	Positive	Positive	Negative	Negative
Pressure	High	High	High	Normal

Definition of Abbreviations: CIE, counterimmunoelectrophoresis; LA, latex agglutination

†CSF glucose concentration should be considered in relation to blood glucose concentration; normally CSF glucose is 50–70% of blood glucose.

- Treatment

Table 22-2. Empiric Antibiotic Therapy Based on Age for Bacterial Meningitis

Age	Most Likely Organisms	Empiric Antibiotics
0-2 months	GBS, *E. coli*, *L. monocytogenes*	Ampicillin + cefotaxime
2-3 months	Above perinatal organisms + some *S. pneumoniae* + very little *H. influenza* type B	Ampicillin + cefotaxime/ ceftriaxone + vancomycin (assume resistant *S. pneumoniae*)
3 months – 2 years	*S. pneumoniae* + *N. meningitides*	Vancomycin + cefotaxime/ ceftriaxone
2-18 years	*N. meningitides* +	Vancomycin + cefotaxime/ ceftriaxone

Data support the use of IV dexamethasone added to the initial treatment of meningitis due to HiB, beginning with the first dose for 4 doses in children age >6 weeks (this will rarely be the case). Decreased incidence of fever, elevated CSF protein, and 8th cranial nerve damage.

- Complications
  - Increased ICP with herniation and seizures
  - Subdural effusion, especially in infants with HiB, can cause **seizures,** persistent fever; drain if symptomatic.
  - Cranial nerve palsies, stroke, thrombosis of dural venous sinuses
  - Most common sequela is **hearing loss** (especially with pneumococcus)
  - Less common: intellectual disability, developmental delay, visual impairment
- Prevention
  - **Chemoprophylaxis with rifampin for *N. meningitidis* and HiB, but not for *S. pneumoniae***
  - All close contacts regardless of age or immune status

Acute Meningococcemia

- Initially may mimic a viral disease (nonspecific)
- Any organ can be affected by **vasculitis and thromboembolic disease.**
- **Characteristic meningococcal rash** (black central arch and surrounding ring or erythema) often seen before more serious signs develop
- If fulminant—rapid progression: **septic shock, disseminated intravascular coagulation, acidosis, adrenal hemorrhage, renal and heart failure**
- Petechiae and purpura ± meningitis = **purpura fulminans (DIC)**
- Need high dose IV penicillin ASAP
- Chemoprophylaxis for close quarters (dorms, army barracks)

Note

Anything that suggests temporal lobe involvement (i.e., focal seizures, CT scan, MRI, and EEG findings localized to the temporal lobe) is highly suspicious for herpes simplex virus.

Note

- Encephalitis = meningitis + mental status changes
- Consider drug ingestion in differential diagnosis

Viral (Aseptic) Meningitis

- Affects meninges and brain tissue variably; most are self-limited; person-to-person contact in summer and fall; most are enteroviruses
  - Arbovirus = arthropod-borne viruses; vectors are mosquitoes and ticks after biting infected birds or small animals; spreads to humans and other vertebrates
  - Rural exposure more common
  - Herpes simplex: **focal**; progresses to coma and death without treatment
  - Varicella zoster: most common presentation is cerebellar ataxia and acute encephalitis.
  - Cytomegalovirus: in immunocompromised, disseminated disease; or congenital infection but not in immunocompetent host
  - Epstein-Barr virus (EBV), mumps: mild but with 8th-nerve damage
- Clinical
  - **Headache and hyperesthesia in older children**
  - **Irritability and lethargy in infants**
  - **Fever, nausea, vomiting, photophobia, and neck, back, and leg pain**
  - Exanthems, especially **echovirus and coxsackie,** varicella, measles, and rubella
- Complications
  - Guillain-Barré syndrome, transverse myelitis, hemiplegia, cerebellar ataxia
  - Most resolve without problems except for neonates with HSV (severe sequelae)
- Diagnosis
  - **PCR of CSF is the best test.**
  - Viral culture
- Treatment—supportive, except acyclovir indicated for herpes simplex virus (HSV)

Clinical Recall

A 5-month-old boy presents to the emergency department with fever, lethargy, and meningismus. A lumbar puncture is performed, and CSF is sent for analysis. What is the best next step in management?

A. Ampicillin and ceftriaxone

B. Ampicillin, ceftriaxone, and vancomycin

C. Ceftriaxone and vancomycin

D. Ampicillin and vancomycin

E. IV fluids, and wait for CSF culture results before initiating antibiotic therapy

Answer: C

Note

Pertussis

Early treatment *may* alter the course of disease. Treatment decreases communicability.

PERTUSSIS

A 10-month-old child who is delayed in immunizations presents with a paroxysmal cough. The patient appears ill and continuously coughs throughout the examination. The patient has facial petechiae and conjunctival hemorrhages. In addition, the patient has post-tussive emesis.

- Cause—*Bordetella pertussis*
  - Endemic; very contagious; aerosol droplets
- Neither natural disease nor vaccination provides complete or lifelong immunity; **wanes after age 8–15 years**
  - Subclinical reinfection
  - Coughing **adolescents and adults are major reservoirs.**
- Clinical presentation of **whooping cough**
  - **Catarrhal phase** (2 weeks)—coldlike symptoms (rhinorrhea, conjunctival injection, cough)
  - **Paroxysmal phase** (2–5 weeks)—increasing to severe coughing paroxysms, inspiratory "whoop" and facial petechiae; post-tussive emesis
  - **Convalescent phase** ≥ 2 weeks of gradual resolution of cough
- Diagnosis
  - **History may reveal incomplete immunizations**
  - **Gold standard is PCR of** nasopharyngeal aspirate 2–4 weeks after onset of cough, or a culture
- Treatment (See immunization chapter)
  - **Supportive care**
  - **Always treat if suspected or confirmed: erythromycin for 14 days** (other macrolides with similar results) only decreases infectious period of patient; it *may* shorten the course of illness; also treat **all household members and any close contacts**

BARTONELLA (CAT-SCRATCH DISEASE)

A 6-year-old presents with a swollen 3×5-cm tender, erythematous, anterior cervical neck node. He denies a history of fever, weight loss, chills, night sweats, or sore throat. The patient's pets include a kitten, a turtle, and goldfish.

- Etiologic agent—*Bartonella henselae*
  - **Most common cause of lymphadenitis lasting >3 weeks**
  - Cutaneous inoculation (arthropod borne by cat flea); kittens transmit better than cats
  - Incubation period 3–30 days
- Clinical presentation
  - One or more 3- to 5-mm **red to white papules along the linear scratch** *plus* hallmark: **chronic regional lymphadenitis**
  - Other nonspecific findings: fever, malaise, headache, anorexia
  - Less common: abdominal pain, weight loss, hepatosplenomegaly, osteolytic lesion
  - Atypical presentation: Parinaud oculoglandular syndrome
- Diagnosis
  - **Clinical with history of scratch from cat**
  - Tissue: **PCR** and Warthin-Starry stain (shows gram-negative bacilli)
  - Serology: variable immunoglobulin IgG and IgM response (not good test)
- Treatment: aspiration of large and painful lesions; usually self-limiting and resolves in 2–4 mos; **avoid antibiotics** unless severe hospitalized case as there is discordance between in vitro and in vivo activity

Note

- **Parinaud oculoglandular syndrome** (similar to conjunctivitis) consists of unilateral conjunctivitis, preauricular lymphadenopathy, and cervical lymphadenopathy.
- It can be transmitted by rubbing the eye after touching a pet.

MYCOBACTERIA

Tuberculosis

A 10-year-old child is referred by the school nurse because of a positive tuberculin skin test. The patient has been well, without any associated complaints.

- ***M. tuberculosis***
- High-risk reservoirs—recent immigrants, low SES, HIV, elderly
- Primary complex—affects the **lung** with local infection with hilar adenopathy
- Latent infection—reactive TB skin test and absence of clinical or radiographic findings
- Diagnosis
  - Skin testing
    - Delayed hypersensitivity—Mantoux (PPD) test, (+) most often 4–8 weeks after inhalation
    - Positive reaction (**5, 10, 15** mm), depending on risk factors
  - Best—if can get sputum
    - **3 consecutive early A.M. gastric aspirates (still only 50%, even with PCR)**
    - A negative culture **never** excludes the diagnosis.
- Clinical Presentation
  - Primary TB usually asymptomatic in children; healthy host will wall off the organism; occasionally, low-grade fever, mild cough, malaise which resolve in 1 week
  - Infants more likely to have signs and symptoms
  - Reactivation rare, (esp. if acquired <2 years of age) occurs during adolescence
  - Small number with extrapulmonary presentation; symptoms depend on location
- Presentation
  - Primary pulmonary disease
    - Localized nonspecific infiltrate
    - Large adenopathy compared to infiltrate: compression → atelectasis and hyperinflation; most resolve completely
- Extrapulmonary
  - Erosion into blood or lymph = miliary
    - Lungs
    - Spleen
    - Liver
    - Bone and joints—Pott disease (destruction of vertebral bodies leading to kyphosis)
    - **TB meningitis**—mostly affects brainstem; CN III, VI, VII palsies and communicating hydrocephalus
  - If reactivation—fever, anorexia, malaise, weight loss, night sweats, productive cough, hemoptysis, chest pain

Note

Mantoux Test Reactions

- Reaction >5 mm is positive in those who have been exposed to TB or are immunocompromised.
- Reaction >10 mm of induration is positive in high-risk people (for those low-risk, >15 mm is positive)

Previous vaccination with bacilli Calmette-Guérin may cause a **false-positive** reaction, while immunocompromisation, malnourishment, or previous vaccination with live virus may cause a **false-negative**. Consider interferon gamma release assay.

- Treatment
  - Latent TB
    - INH × 9 months
  - Primary pulmonary disease
    - INH + rifampin × 6 months, plus pyrazinamide in first 2 months
  - Increased community resistance
    - Add streptomycin, ethambutol or ethionamide
  - In some cases of meningitis, studies have shown decreased morbidity and mortality when **corticosteroids** added to regimen. Use adjunctively in patients with severe miliary disease and pericardial or pleural effusions.

Bacille Calmette-Guérin (BCG) Vaccination in the United States

- **Not routine**—variable efficacy, time-limited efficacy
- Only used in the following situations:
  - High-risk with close or long-term exposures
  - Continuous exposure to resistance strains
- Contraindicated in those with primary or secondary immune deficiencies

Perinatal Tuberculosis

- If mother has (+) PPD → obtain chest x-ray
- Start INH after first trimester if chest x-ray (–) and clinically stable → no separation, no evaluation of baby, INH prophylaxis for mother for 9 months
- If mother has suspected TB at delivery → separate baby from mother until chest x-ray obtained
  - If mother has disease → treat infant for TB with no further separation from mother and treat mother with anti-TB therapy until mother is culture negative for 3 months

LYME DISEASE

A 6-year-old child presents with a rash after camping on Long Island with his family. On physical examination, the rash has a red raised border with central clearing.

Borrelia burgdorferi

- Most common vector-borne disease in the United States
- Most in southern New England, eastern Middle Atlantic states, and upper Midwest, with small endemic area along the Pacific coast
- *Ixodes scapularis,* i.e., the deer tick
- Clinical presentation: history of tick bite is helpful but absent in most; tick is small and often not seen by human eye; history of being in the woods or mountains should give suspicion

  - Early disease
    - **Local: erythema migrans** 3–32 days after bite at site of the bite; **target lesion (must be >10 cm in diameter)** often called "bulls-eye" rash; fever, headache, and malaise most common symptoms; without treatment, lesion resolves in 1–2 weeks
    - **Early disseminated: secondary lesions**, smaller than the primary + constitutional symptoms + lymphadenopathy; uveitis and Bell palsy (may be only finding); carditis (myocarditis, heart block); CNS findings (neuropathy, aseptic meningitis)
  - Late disease: **arthritis** weeks to months later; affecting large joints, more likely to be chronic in adults
- Diagnosis
  - No definitive tests
  - Primarily **clinical and based on history + rash**
  - **Quantitative ELISA test and confirmatory Western blot if the ELISA is positive or equivocal**
- Treatment
  - Early: **doxycycline** 14–21 days (if age >8); **amoxicillin** (if age <8)
  - Ceftriaxone with meningitis or carditis (heart block)
  - Doxycycline or amoxicillin with Bell palsy
- Prognosis—excellent in children with permanent cure

Clinical Recall

For which of the following patients with Lyme disease is the correct treatment listed?

A. A 10-year-old boy with erythema migrans: doxycycline

B. A 5-year-old girl with meningitis: amoxicillin

C. A 2-year-old boy with erythema migrans: ceftriaxone

D. An 11-year-girl with carditis: doxycycline

E. An 8-year-old boy with Bell palsy: ceftriaxone

Answer: A

ROCKY MOUNTAIN SPOTTED FEVER

A 17-year-old presents to the emergency department with his friends because of fever, headache, and a rose-colored rash that began on his ankles and is spreading. The patient and his friends have been camping in Virginia.

Rickettsia rickettsii

- Consider in differential diagnosis of **fever, headache, and rash in summer months, especially after tick exposure**
- Seen now in every state; most in Southeast, especially in **North Carolina**
- Wooded areas, coastal grasses, and salt marshes
- Most April–September; most patients age <10 years
- Ticks are the natural hosts, reservoirs, and vectors (dog tick, wood tick, brown dog tick).
- Clinical presentation
  - Incubation period 2–14 days, then headache, fever, anorexia, myalgias, gastrointestinal (GI) symptoms early
  - After third day—**skin rash**
    - Extremities first (palms, soles)
    - Spreads rapidly
    - Becomes petechial/hemorrhagic
    - Palpable purpura
  - Vascular obstruction, **due to vasculitis and thromboses, leads to gangrene**
  - Hepatosplenomegaly
  - CNS: delirium, coma, and other neurologic findings
  - Myocarditis, acute renal failure, pneumonitis, shock
  - Severe or fatal disease usually due to delay in diagnosis and treatment
- Diagnosis
  - **Strong clinical suspicion**
  - **Confirm with serologic tests;** fourfold increase in antibody titer (acute, convalescence)
- Treatment—**doxycycline or tetracycline in all patients regardless of age** (chloramphenicol in allergy only)

MYCOTIC INFECTIONS

Candida

A newborn infant is noted to have white plaques on his buccal mucosa that are difficult to scrape off with a tongue depressor. When removed, a small amount of bleeding is noted by the nurse. The infant just received a course of empiric antibiotics for suspected Group B β-hemolytic *Streptococcus* infection.

- Most human infections with *C. albicans;* part of normal gastrointestinal tract and vaginal flora of adults
- Oral infection = **thrush;** white plaques; seen with **recurrent or continuing antibiotic treatment and immunodeficiency and normally in breast-fed infants**
  - Diagnosis—**punctate bleeding with scraping**
  - Treatment—oral **nystatin;** if recalcitrant or recurrent, single-dose fluconazole

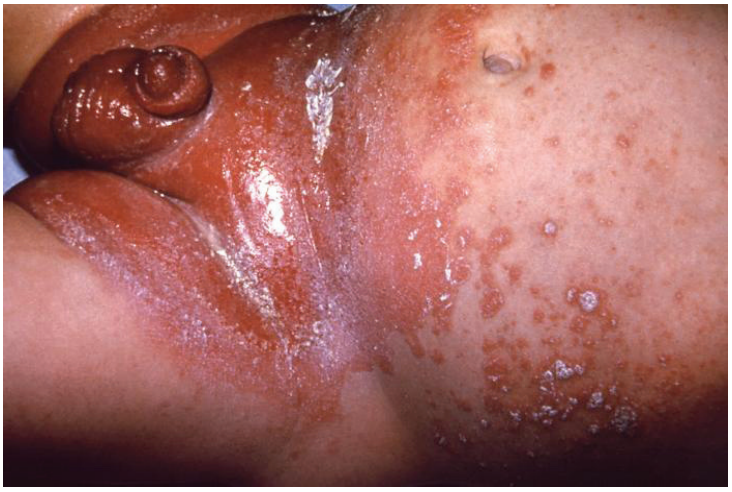

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Figure 22-1. Diaper Rash Secondary to *Candida albicans* Infection

- Diaper dermatitis: intertriginous areas of perineum; confluent, papular erythema with **satellite lesions**
  - Diagnosis—skin scrapings; see yeast with KOH prep, but not usually necessary in the presence of clinical findings
  - Treatment—**topical nystatin;** if significant inflammation, add 1% hydrocortisone for 1–2 days
- **Catheter-related fungemia** can affect any organ; may look like bacterial sepsis
  - Diagnosis—buffy coat, catheter tips, urine shows yeast, culture
  - Treatment—remove all catheters; **amphotericin B is drug of choice**
- Chronic mucocutaneous candidiasis—primary defect of T lymphocytes in response to *Candida*; often when **endocrine (diabetes mellitus) and autoimmune disease**

Cryptococcus neoformans

- Soil contaminated with bird droppings, or in fruits and vegetables
- Predominant fungal infection in **HIV** patients; rare in children and immunocompetent
- Inhalation of spores; in immunocompromised (mostly in HIV patients) disseminated to **brain, meninges**, skin, eyes, and skeletal system; forms granulomas
- **Pneumonia most common presentation**; asymptomatic in many; otherwise, progressive pulmonary disease
- Diagnosis
  - **Latex agglutination—cryptococcal antigen in serum**; most useful for CSF infections
- Treatment
  - Oral fluconazole for 3–6 months if immunocompetent and only mild disease
  - Amphotericin B + flucytosine if otherwise
  - In HIV—lifelong prophylaxis with fluconazole

Coccidioidomycosis (San Joaquin Fever; Valley Fever)

A 14-year-old who lives in Arizona presents to the physician with a 10-day history of fever, headache, malaise, chest pain, and dry cough. He is currently in New York visiting relatives and is accompanied by his aunt. Physical examination reveals a maculopapular rash and tibial erythema nodosum.

- Inhaled arthroconidia from dust; no person-to-person spread
- Types
  - Primary (self-limiting)
  - Residual pulmonary lesions (transient cavity or chest x-ray)
  - Disseminating—can be fatal; more common in males, Filipino/Asians, blood group B
    - Influenza-like symptoms
    - Chest pain
  - **Dry, nonproductive cough**
    - Maculopapular rash
    - **Tibial erythema nodosum**
- Diagnosis
  - Sputum should be obtained via bronchoalveolar lavage or gastric aspirates.
  - Diagnosis is confirmed by culture, **PCR**
- Treatment—most conservative; for those at high risk of severe disease, treatment as with histoplasmosis

Note

Disseminated Coccidiomycosis Triad

- Flu-like symptoms +/– chest pain
- Maculopapular rash
- Erythema nodosum

VIRAL INFECTIONS

Viral Exanthematous Disease

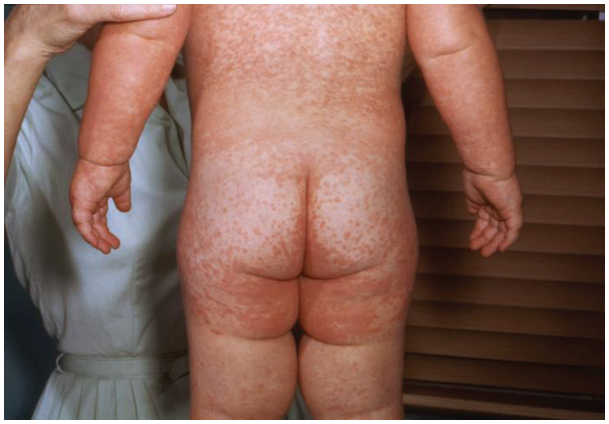

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Figure 22-2. Typical Appearance of Morbilliform Rash Seen in Measles Infection

Measles

A mother presents to the physician with her adopted daughter, who has just arrived in the United States from a foreign country. The immunization record is not up-to-date. The child has coryza, cough, conjunctivitis, and fever. The mother states that the child also has a rash that began cephalad and spread caudad. On physical examination, a morbilliform rash is seen over the body including the palms. Tiny grayish white dots are seen on the buccal mucosa next to the third molar.

- Rubeola—10-day measles
- RNA *Paramyxovirus*, **very contagious**
- Risk factors—Unimmunized entering high school or college
- Incubation—10–12 days before prodrome appears
- Prodrome—3 Cs
  - Cough
  - Coryza
  - Conjunctivitis, then Koplik spots (grayish-white spots on buccal mucosa)
- Final—rash + fever (occur concurrently)
  - Rash—macular; starts at head (nape of neck and behind ears) and spreads downward; fades in same manner
- Diagnosis—mainly clinical
- Treatment—supportive, vitamin A (if deficient)
- Complications—otitis media (most common), pneumonia, encephalitis
- Prevention—immunization

Rubella

A 5-year-old child who has delayed immunizations presents with low-grade fever, a pinpoint rash, postoccipital and retroauricular lymphadenopathy, and rose spots on the soft palate.

- German, 3-day measles
- Risk factors/Etiology—Incubation 14–21 days; contagious 2 days before rash and 5–7 days after rash
- Clinical Presentation
  - Rash similar to measles, **begins on face** and spreads to rest of body, lasts approximately 3 days; concurrent with fever
  - **Retroauricular, posterior, and occipital lymphadenitis** are hallmarks.
  - Forschheimer spots—affect the soft palate and may appear before onset of the rash
  - Polyarthritis (hands) may occur in some patients, especially older females.
- Diagnosis—clinical
- Treatment—supportive
- Prevention—immunization with MMR vaccine
- Complications—congenital rubella syndrome seen if contracted during pregnancy (*see* Newborn chapter)

Roseola

A 15-month-old infant is brought to the physician because of a rash. The mother states that the patient had a fever of 40 C (104 F) for the last 3 days without any source of infection. She explains that the fever has resolved, but now the child has pink, slightly raised lesions on the trunk, upper extremities, face, and neck.

- Also known as exanthema subitum
- Etiology—febrile illness of viral etiology; due to infection with human herpes virus—HHV-6; peaks in children age <5 years, usually 6–15 months; incubation period 5–15 days
- Clinical Presentation
  - High fever (up to 41 C [106 F]) lasting a few days with only signs and symptoms of URI
  - By day 3 or 4, the fever resolves and a maculopapular rash appears on the trunk, arms, neck, and face
    - Characteristic rose-colored rash begins as papules
- Diagnosis and treatment—clinical diagnosis based on age, history, and physical findings. No studies necessary and treatment is supportive.

Mumps

A 4-year-old child is brought to the clinic by his mother with a history of swelling in his face and fever for the last 4 days. His history includes incomplete immunizations due to religious beliefs. Physical examination reveals bilateral, tender facial swelling around the area of the masseter muscle and fever of 39.3 C (102.7 F).

- Etiology/Risk Factors—viral infection due to *Paramyxovirus* transmitted through airborne droplets and respiratory/oral secretions.,
  - Most common in winter/spring
  - Incubation period from 14–24 days
  - Contagious 1 day before and 3 days after swelling appears
  - History usually reveals inadequate or lacking immunizations
- Clinical Presentation
  - Constitutional findings: fever, headache, and malaise
  - Unilateral or bilateral salivary gland swelling, predominantly in the parotids
  - Orchitis (and oophoritis) possible, rare before puberty
    - May result in sterility only if **bilateral**
- Diagnosis—clinical and based upon history/physical findings
- Treatment—supportive
- Meningoencephalomyelitis most common complication; others include pancreatitis, thyroiditis, myocarditis, deafness, and dacryoadenitis

Varicella

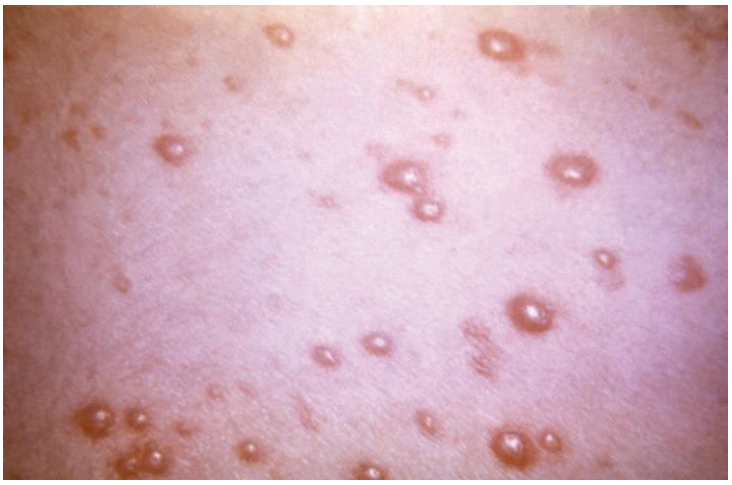

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Figure 22-3. ChickenPox is Characterized by Macules, Papules, Vesicles, and Crusts in Varying Stages of Healing

A 5-year-old child is brought to the emergency center because he has a temperature of 38.9 C (102 F) and is developing a pruritic rash. The rash appears to be in various stages of papules, vesicles, and crusts. It began on his trunk and spread to his extremities.

- Etiology/Risk Factors—due to varicella-zoster virus, a herpes virus
  - Incubation 10–21 days
  - Transmitted through respiratory secretions
  - Remains latent in sensory ganglia after recovery → reactivation in immunosuppressed
- Clinical Presentation—nonspecific symptoms and fever preceding rash
  - **Pruritic rash in various stages**
    - **Macules → papules → vesicle → open vesicle → crust**
    - Lesions can turn hemorrhagic.
    - **Crops of lesions at same time**
- Clinical diagnosis—no labs
- Treatment
  - Supportive in immunocompetent; treat secondary infection
  - Consider acyclovir and VZIG in immunocomprised or those at risk for severe disease
- Complications—worse in adolescence (scarring)
  - Varicella pneumonia seen in 15–20%
  - Other sequelae include Guillain-Barré syndrome, encephalitis, cerebellar ataxia, postherpetic neuralgia, and Ramsay-Hunt syndrome.
  - Congenital varicella (*see* Newborn chapter)
- Prevention—second vaccine dose recommended

Erythema infectiosum (fifth disease)

A 4-year-old is brought to the physician's office because she developed red cheeks that appear as if someone has slapped her and a lacy rash on her upper extremities and trunk.

- Etiology—due to Parvovirus B19, a DNA virus; seen most commonly in spring
- Clinical Presentation
  - Mild systemic symptoms
  - Arthritis
  - Intensely red "slapped cheek" appearance
  - Lacy, reticular rash over trunk and extremities
  - Sparing of palms and soles
  - Rash may last up to 40 days
- Diagnosis—clinical; labs not routine **except** when diagnosing hydrops, then viral DNA in fetal blood is often helpful
- Complications—aplastic crisis in patients with hemolytic anemia; hydrops fetalis in neonates during maternal infection in first trimester

Clinical Recall

An unimmunized 6-year-old boy presents with a rash. Which of the following favors a diagnosis of measles?

A. Retroauricular lymphadenitis

B. Maculopapular rash that includes the hands and feet

C. Lacy, reticular rash over the trunk and extremities

D. Macular rash on the neck that has spread down to the trunk

E. Vesicular rash with interspersed crusted lesions

Answer: D

Table 22-3. Common Childhood Infections with Exanthems

	Prodrome	Enanthem	Exanthem	Complications
Measles	• Cough • Coryza • Conjunctivitis • High fever	Koplik spots	Macules: hairline, face, neck → trunk and extremities	• Otitis media • Pneumonia • Encephalitis • Subacute sclerosing panencephalitis
Rubella	Mild constitutional symptoms	Forschheimer spots	• Similar to measles • Posterior cervical & auricular nodes	Congenital rubella–teratogenic
Mumps	• Headache • Fever • Malaise • Muscle pain	Glandular swelling	Swollen parotid & submandibular glands	• Encephalitis • Orchitis • Pancreatitis
Varicella	• Low-grade fever • Malaise • URI symptoms	None	• Crops of papules, vesicles • Crusts at same time • Central to peripheral	• Superinfection • Zoster • Pneumonia • Hepatitis • Encephalitis • Congenital varicella
Fifth Disease	Mild URI symptoms	None	Slapped cheek → trunk → central clearing-lacey	Aplastic anemia
Roseola	• URI symptoms • Abrupt onset • High fever then breaks	None	Fever falls rapidly → fine macular rash on trunk and spreads to extremities	Febrile seizures
Scarlet Fever	Sore throat	• Exudative pharyngitis • Strawberry tongue	• Fine maculopapular rash (feels like sand paper, especially in antecubital and inguinal areas) • Pastia lines	• Acute rheumatic fever • Glomerulonephritis

OTHER VIRAL DISEASES

Epstein-Barr Virus

A 22-year-old college student presents to the clinic complaining of fever, fatigue, and sore throat that have not improved for the last 2 weeks. Physical examination reveals generalized adenopathy most prominent in the anterior and posterior cervical nodes.

- Etiology/Risk Factors
  - **Infectious mononucleosis** (90%)
  - First human virus to be associated with **malignancy**
    - Nasopharyngeal carcinoma
    - **Burkitt lymphoma**
    - Others: Hodgkin disease, lymphoproliferative disorders, and leiomyosarcoma in immunodeficiency states
  - Transmitted in **oral secretions** by close contact (kissing disease); **intermittent shedding for life**
  - Incubation period: 30–50 days; most cases in infants and young children are clinically silent
- Clinical presentation
  - Insidious, vague onset: prodrome for 1–2 weeks with fever, fatigue, headache, myalgia, sore throat, abdominal pain
  - Generalized lymphadenopathy (most **in anterior and posterior cervical** and submandibular nodes; less often in axillary, inguinal, **epitrochlear** nodes), splenomegaly (half the cases; 2–3 cm), and a small number with hepatomegaly
  - Moderate to severe pharyngitis with tonsillar exudative enlargement
  - Small number with rashes (maculopapular); most will have rash if treated with **ampicillin or amoxicillin** (immune-mediated vasculitic rash)
- Diagnosis
  - **Atypical lymphocytosis**
  - **Heterophile antibodies (Monospot test)**
  - **IgM to viral capsid (IgM–VcA–EBV) antigen is the most valuable and specific (up to 4 months).**
- Treatment
  - Rest and symptomatic therapy
  - **No contact sports or strenuous activity with splenomegaly**
  - Short course of **steroids** for complications: incipient airway obstruction, thrombocytopenia with hemorrhage, autoimmune hemolytic anemia, seizures, meningitis
- Complications
  - **Splenic hemorrhage or rupture** (very rare); most in second week, most with trauma
  - Swelling of tonsils and oropharyngeal lymphoid tissue: **airway obstruction**
  - Neurological complications rare; Guillain-Barré syndrome
  - Aplastic anemia

Note

Infectious Mononucleosis Triad

- Fatigue
- Pharyngitis
- Generalized adenopathy

Note

For any exam question that mentions onset of rash **after** taking ampicillin or amoxicillin for URI-related symptoms, think mono first.

  - Interstitial pneumonia
  - Myocarditis
- Prognosis
  - Most cases resolve in 2–4 weeks; some disability that comes and goes for a few months is common; and there may be fatigue for a few years
  - There is no evidence of second attacks from EBV and no evidence that EBV is related to chronic fatigue syndrome

Influenza Viruses

A 14-year-old girl is brought to the physician's office by her mother. She has a 2-day history of fever of 39.7 C (103.5 F), headache, sore throat, refusal to eat, myalgia, chills and non-productive cough. Her current temperature in the clinic is 39.3 C (102.7 F).

- Etiology/Risk Factors
  - Three types—A, B, and C, with A and B being the primary pathogens of epidemic disease; now, also since 2009, H_1N_1
  - Migratory avian hosts may be responsible for spread.
  - Annual spread between Northern and Southern hemispheres; origin of new strains often traced to Asia
  - One or 2 predominant strains spread annually
  - Attack rate highest in the **young**; colder months in temperate climates
  - Transmission by small particle aerosol
- Clinical presentation
  - Predominantly respiratory illness
  - **Abrupt onset** with coryza, conjunctivitis, pharyngitis, and **dry cough**
  - Prominent systemic signs: **fever (2–4 days), myalgia, malaise, headache**
- Diagnosis
  - Virus can be isolated from nasopharynx early in course.
  - Rapid diagnostic test: **ELISA**
  - Can be confirmed serologically with acute and convalescent titers or PCR
- Treatment
  - Rest and adequate fluid intake
  - Control of fever
  - Antiviral drugs: decrease severity and duration if administered within first 48 hours of symptoms
- Complications—otitis media, pneumonia; secondary bacterial infection, myocarditis

Coxsackievirus

A 2-year-old infant is brought to the clinic with a vesicular rash in his mouth and on his palms and soles. Examination reveals a rash on his buttocks.

- Etiology/Risk Factors—due to infection with coxsackievirus A16
- Clinical diagnosis: Characteristic lesions—seen anywhere but especially on the oral mucosa, hands and feet; hand-foot-mouth disease. Rash on the buttocks is common.
- Coxsackievirus B also responsible for viral myocarditis
- Treatment is supportive care

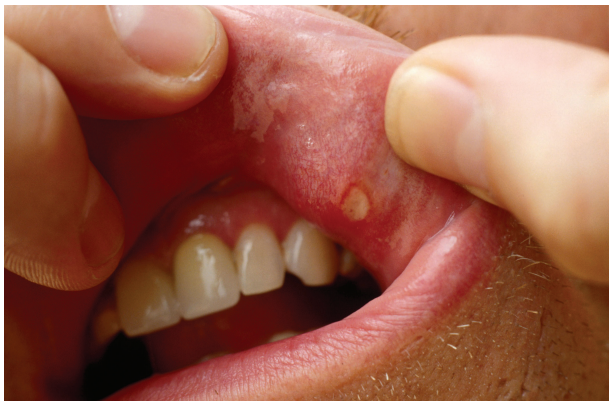

Figure 22-4. Oral Ulcers of Hand-Foot-and-Mouth Disease

Adenovirus

A 12-year-old patient presents with fever, sore throat, and follicular conjunctivitis.

- Etiology/Risk Factors—DNA virus responsible for URIs in infants and children
- Clinical Presentation—Fever, pharyngitis, conjunctivitis, and diarrhea are common.
  - Less common features include pharyngoconjunctival fever, myocarditis, and intussusception.
- Diagnosis—serology, viral culture, or PCR, but not usually necessary
- Treatment—supportive

Poliovirus

- Etiology/Risk Factors—lives in gastrointestinal track
- Clinical Presentation—can cause URI symptoms
  - Paralytic polio
    - Asymmetric flaccid paralysis
- Prevent with vaccination

Acquired Immunodeficiency Syndrome (AIDS)

An 18-month-old has failure to thrive and developmental delay. The patient also has a history of recurrent ear infections, oral thrush, and chronic diarrhea. The patient on physical examination today is noted to have lymphadenopathy.

- Etiology/Risk Factors
  - Most are children born in developing countries; acquired at birth from an HIV-positive mother
  - Breastfeeding in developing countries is an important route of transmission.
  - Pregnant females in United States and other developed countries are routinely screened for HIV infection in prenatal labs, unless the patient refuses.
    - Early treatment and prevention of neonatal infection through anti-retroviral therapy and preventive measures during delivery/postpartum period
- Clinical presentation
  - HIV-infected newborns: rapid onset of symptoms and AIDS in first few months of life
  - Initial symptoms may include
    - Lymphadenopathy
    - Hepatosplenomegaly
    - Failure to thrive
    - Chronic diarrhea
    - Interstitial pneumonia
    - Oral thrush
  - Children > adults: recurrent bacterial infections, chronic parotid swelling, lymphocytic interstitial pneumonitis, early progressive neurological deterioration
- Infections
  - **Recurrent bacterial infections with encapsulated organisms and other gram-positive and gram-negative organisms**
  - **Opportunistic infections**; most common is PCP (onset of fever, tachypnea, dyspnea, and marked hypoxemia)
  - ***Mycobacterium avian*-intracellulare complex**: disseminated disease in severely compromised
  - Oral candidiasis and other invasive fungal infections
  - Viral infections, especially herpes group
- Other problems
  - CNS disease
  - Cardiomyopathy
  - Enteropathy
  - Wasting syndrome, nephropathy
  - Many cutaneous manifestations
  - All hematologic manifestations, malignancies

- Diagnosis
  - **HIV-DNA by PCR**
  - Maternal HIV IgG antibodies cross the placenta
    - Screen will be positive in **all** newborns up to age 18 months so need 2 of 3 ⊕ PCR for HIV in first month of life.
  - In any **child >18 months of age**: test for infection through **IgG Ab by ELISA and then confirm with Western blot to establish the diagnosis.**
- Treatment—infants born to HIV-infected mothers
  - Mother should be on **perinatal triple anti-retroviral** therapy and then IV ZDV at start of labor until cord is clamped
  - Infant **should be started on ZDV (birth)** until neonatal disease is excluded
    - Also start **PCP prophylaxis (TMP-SMZ) at 1 month** until disease excluded
    - Follow CBC, platelets, CD4 and CD8 counts
    - With symptoms or evidence of immune dysfunction, should be treated with **antiretroviral therapy, regardless of age or viral load**
- Prognosis
  - Best single prognostic indicator is the **plasma viral load.**
  - Mortality higher with **CD4 count <15%**
  - Poor prognosis with persistent fever and/or thrush, serious bacterial infection (meningitis), hepatitis, persistent anemia, and/or thrombocytopenia (30% die by age 3)
  - Children with opportunistic infection, encephalopathy, or wasting syndrome have the worst prognosis (75% die by age <3)

Clinical Recall

Which of the following best supports a diagnosis of coxsackie virus A?

A. New rash after treatment with amoxicillin

B. Diffuse rash with ulcerative lesions in the mouth

C. Myalgias, fever, and dry cough of abrupt onset

D. Chest pain and myocardial infection

E. Diarrhea and pharyngitis

Answer: B

HELMINTHIC DISEASES

Ascariasis

A child is brought to the physician's office because his mother found a "worm" while changing his diaper. He also has a chronic cough with pinkish sputum.

- Etiology/Pathogenesis—*Ascaris lumbricoides;* nematode (roundworm)
  - Most prevalent human helminth in the world
  - High prevalence in poor socioeconomic status countries, with use of human waste as fertilizer, and with geophagia (highest in preschool age)
  - Travels to the small intestines → releases larvae → migrates through venous circulation to lungs **and causes pulmonary ascariasis (Loeffler syndrome)** → through alveoli and bronchi to trachea and are swallowed mature in intestine to adult worms
- Clinical Presentation—most asymptomatic or mild
  - **Most common symptom is pulmonary disease—cough and blood-stained sputum**
  - Followed by obstructive intestinal or biliary tract disease
    - May have colicky abdominal pain or bile-stained emesis
  - CBC reveals **significant blood eosinophilia**
  - Can be identified on fecal smear
- Treatment—**albendazole,** mebendazole, or pyrantel pamoate

Note

Loeffler syndrome = pulmonary ascariasis plus hemoptysis

Hookworm

A 5-year-old girl is brought to the physician due to lack of appetite, abdominal pain, and diarrhea. On physical examination a yellow-green pallor is noted.

- Etiology/Risk Factors—*Ancylostoma duodenale* and *Necator americanus* are nematodes transmitted through warm, moist soil; usually in rural areas where human waste is used as fertilizer.
  - Penetrate **through the skin** (leads to intense pruritis at site of entry) or are ingested
  - Migration through veins to lungs and are swallowed → have teeth to attach to mucosa and can remain up to 5 years, where they mate and produce eggs
- Clinical Presentation—Morbidity from **blood loss**
  - **Iron deficiency anemia**
  - Hypoalbuminemia → edema**,** anasarca
  - Also, cough, colicky abdominal pain, anorexia, diarrhea
  - Physical growth retardation, cognitive and intellectual deficits
  - Green-yellow skin discoloration known as **chlorosis** and seen in chronic infection
  - Labs reveal significant **blood eosinophilia**.
  - Eggs can be identified on fecal smear.
- Treatment—**mebendazole or albendazole** is drug of choice; pyrantel pamoate an alternative
  - **Ferrous sulfate** if iron deficient

Note

Most parasites, ova, and cysts can be identified on fecal smear.

Enterobiasis

A mother brings her 4-year-old child to the physician with a history of always scratching her anus. The mother is embarrassed by this behavior. The child attends daycare and loves to play in the sandbox.

- Etiology—*Enterobius vermicularis* is the parasite implicated in pinworm infection.
  - Small, white, threadlike nematodes
  - Most common helminth in the United States
  - Primarily in institutional/family settings that include children; highest at age 5–14
  - Eggs are ingested from being carried on fingernails, clothing, bedding, or house dust; after ingestion, adult worms within 1–2 months
  - Inhabits cecum, appendix, ileus, and ascending colon; **female migration at night to deposit eggs on perianal region and perineum**
- Clinical Presentation—most common symptoms include **itching and restless sleep** and *no* eosinophilia
- Diagnosis—history and use of **adhesive cellophane tape** (tape test) **at night when child is asleep**
- Treatment—infected person and entire family receive **single oral dose of mebendazole and repeat in 2 weeks**

Adolescence 23

Learning Objectives

- ❏ Describe the epidemiology including morbidity and mortality of diseases of adolescence
- ❏ Answer questions related to adolescent sexuality and sexually transmitted diseases
- ❏ Describe the causes and treatments of acne

MORTALITY/MORBIDITY, SEXUALITY, AND STIs

A 14-year-old girl who has not yet achieved menarche presents to the physician with her concerned mother. The mother is afraid that her daughter is not "normal." Physical examination reveals a well-nourished girl in the 50th percentile for height and weight. Breast examination shows an enlarged areolar diameter but no separation of contours. Pubic hair is increased in amount and curled but not coarse in texture. The mother and her daughter wait anxiously for your opinion.

Adolescence and Puberty

Adolescence is the period bridging childhood and adulthood. It begins at age 11–12 years and ends at age 18–21. It includes puberty, which is the process when a child matures into an adult capable of sexual reproduction.

The physical and psychological changes that occur at this time include **completed pubertal/somatic growth** and **social/cognitive/emotional development**, moving from concrete to abstract thinking, establishing an independent identity, and preparing for a career.

All adolescents are at increased risk of mortality and morbidity.

- **Mortality:** accidents, especially motor vehicle; suicide (boys are more successful); homicide (more likely in blacks); and cancer (Hodgkin lymphoma, bone, CNS)
- **Morbidity:** unintended pregnancy; STIs; smoking; depression; crime

There are 3 stages of adolescence.

- **Early (age 10-14 years)**
  - Physical changes (puberty) including rapid growth, puberty including development of secondary sexual characteristics
  - Compare themselves to peers (develop body image and self-esteem)
  - Concrete thinkers and feel awkward

- **Middle (age 15-16 years)**
  - More independent and have sense of identity
  - Mood swings are common
  - Develop abstract thinking
  - Develop relationships that are one-sided and narcissistic
- **Late (age >17 years)**
  - Less self-centered
  - Develop relationships with individuals rather than groups
  - Contemplate future goals, plans, careers
  - Idealistic; have a sense of right and wrong

While puberty is irreversible, there is variability in its onset and duration. There is, however, no variability in the *order* of the changes, ie, physical changes during this time reflect hormonal changes in the body.

Because puberty occurs at an individual rate, an accepted scale to determine progression is the **Tanner stage scale**, identifying stages of development rather than age.

Variants of development are normal and most cases require only **reassurance** to the patient and family. For example, breast asymmetry and gynecomastia are often seen in boys at Tanner stage 3, and irregular menses due to anovulatory cycles are often seen in girls starting to menstruate.

Table 23-1. Tanner Stages of Development (Sexual Maturity Rating)

	Female	Both	Male
Stage	Breast	Pubic hair	Genitalia
I	Preadolescent	None	Childhood size
II	Breast bud	Sparse, long, straight	Enlargement of scrotum/testes
III	Areolar diameter enlarges	Darker, curling, increased amount	Penis grows in length; testes continue to enlarge
IV	Secondary mound; separation of contours	Coarse, curly, adult type	Penis grows in length/ breadth; scrotum darkens, testes enlarge
V	Mature female	Adult, extends to thighs	Adult shape/size

Sexually Transmitted Infections

Gonorrhea

A 16-year-old girl presents with fever, chills, pain, and swelling in the small joints of her hands and a maculopapular rash on her upper and lower extremities.

- *Neisseria gonorrhoeae* usually infects mucosal membranes of the genitourinary tract and less commonly the oropharynx, rectum, and conjunctiva.
- Clinical presentation includes urethritis, cervicitis, and dysuria.
- Asymptomatic patients are at higher risk for dissemination, including fever, chills, and arthritis.
- Physical examination
  - Males present with dysuria and purulent penile discharge.
  - Females present with purulent vaginal discharge, cervicitis, abdominal pain, and/or dysuria.
  - Rectal gonorrhea may present with proctitis, rectal bleeding, anal discharge, and/or constipation.
- Tests: culture from discharge; blood culture if dissemination is suspected; Gram stain may show intracellular diplococci
- Check for other STIs, including **syphilis** and **HIV infection**.
- Treatment: single-dose ceftriaxone or azithromycin (treat partners); alternatively, doxycycline for 7 days but **not age <9**

Note

Untreated gonorrhea/Chlamydia may result in PID and/or infertility (due to tubal scarring).

Chlamydia

A 16-year-old boy presents to the emergency department with a persistent penile discharge. The patient states that one week ago he saw his family physician for this same problem, and received an IM shot of penicillin. However, the discharge has not resolved, and he would like a second opinion.

- Cause of nongonococcal urethritis
- Intracellular obligate parasites
- Most common STI in developed countries
- Mucoid discharge (mostly females) or lymphogranuloma venereum
- Tests: nucleic acid amplification (**PCR, ELISA**); culture of infected tissue
- Treatment: single-dose azithromycin or doxycycline for 7 days; erythromycin if pregnant

Trichomonas

A 15-year-old presents to her physician with a yellow, foul-smelling vaginal discharge. On physical examination, she is noted to have a "strawberry cervix."

- *Trichomonas vaginalis* is a protozoan resulting in vaginitis
- Girls with multiple sexual partners are at high risk (though this true of all STIs)
- Frothy, foul-smelling vaginal discharge; males asymptomatic
- "Strawberry cervix" due to hemorrhages in the mucosa
- In females, wet prep shows motile protozoans; in males, examine urine sediment after prostatic massage
- Treat with metronidazole

Herpes

A 17-year-old, sexually active boy presents to the physician because of painful ulcerations on his glans penis and on the shaft of his penis. He has multiple sexual partners and does not use condoms. Fever and inguinal adenopathy are also present.

- HSV 1: nongenital infections of mouth, eye, and lips most common
- HSV 2: genital, neonatal, oral
  - Cervix primary site in girls; penis in boys
  - Tzanck prep—giant multinuclear cells
  - ELISA testing
- Treat with acyclovir, valacyclovir, famciclovir

Table 23-2. Distinguishing Features of Vaginal Discharge

Feature	Bacterial vaginosis	Trichomoniasis	Candida	Chlamydia/ gonorrhea
Discharge	Profuse, malodorous, "fishy"	Gray-green, frothy	Cottage cheese	Purulent
Wet prep	Clue cells, "whiff test" with KOH	Motile Trichomonads	Hyphae seen with KOH prep	WBCs
pH	>4.5	>5	<4.5	—
STI	No	Yes	No	Yes

Clinical Recall

An 18-year-old girl presents with abdominal pain and gray-green vaginal discharge. Motile trichomonads are visualized on wet prep. What is the treatment of choice?

A. Metronidazole

B. Acyclovir

C. Azithromycin

D. Ceftriaxone and azithromycin

E. Clotrimazole

Answer: A

ACNE

A mother brings her 15-year-old daughter to the dermatologist because she has developed pimples. The mother says that her daughter's face "breaks out" because she drinks soda pop. The daughter is argumentative about this but admits that she does drink soda pop every day at lunch. The mother would like you to tell her daughter to stop drinking soda pop. On physical examination, the patient has open and closed comedones and pimples on her forehead, nose, and cheeks.

- Pathogenesis
  - Due to the bacteria—*Propionibacterium acnes*, which forms free fatty acids within the sebaceous follicle
  - Abnormal keratinization of follicular epithelium and impaction of keratinized cells in sebaceous follicles
  - Increased sebum production—At puberty, significant increase in sebum from increased **adrenal androgens** (mostly DHEAS with some role of testosterone and estrogen)
  - Inflammation from lysosomal enzymes, which phagocytose bacteria
- Description: an **open comedone** is a blackhead, while a **closed comedone** is a whitehead (more commonly becomes inflammatory)
  - If comedones rupture, inflammatory lesion and contents spill into adjacent dermis; if close to the surface, forms a **papule or pustule**; if deeper, forms a **nodule**
  - With suppuration → giant-cell reaction to keratin and hair; forms **nodulocystic lesion**
- Treatment must be individualized.
  - Cleansing of skin with mild soap
  - Topical therapy for treatment of comedones and papulopustular acne: **benzoyl peroxide; tretinoin** (Retin-A) **most effective agent for comedonal acne; adapalene** (Differin gel); antibiotics (**erythromycin, clindamycin**)

Note

Isotretinoin is very **teratogenic** and contraindicated in pregnancy.

- Systemic therapy for those who do not respond to topical agents.
  - Antibiotics: especially **tetracycline,** minocycline, doxycycline, erythromycin, clindamycin
  - **Isotretinoin**: for **moderate to severe nodulocystic disease.** Very **teratogenic** (contraindicated in pregnancy) and may cause increased **triglycerides/ cholesterol**, so rule out liver disease beforehand and check triglycerides 4 wks post-treatment
  - **A trial of hormonal therapy can be used in those who are not candidates for isotretinoin.**
- Corticosteroid injections to aid in healing painful nodulocystic lesions.
- Dermabrasion to decrease visible scarring.

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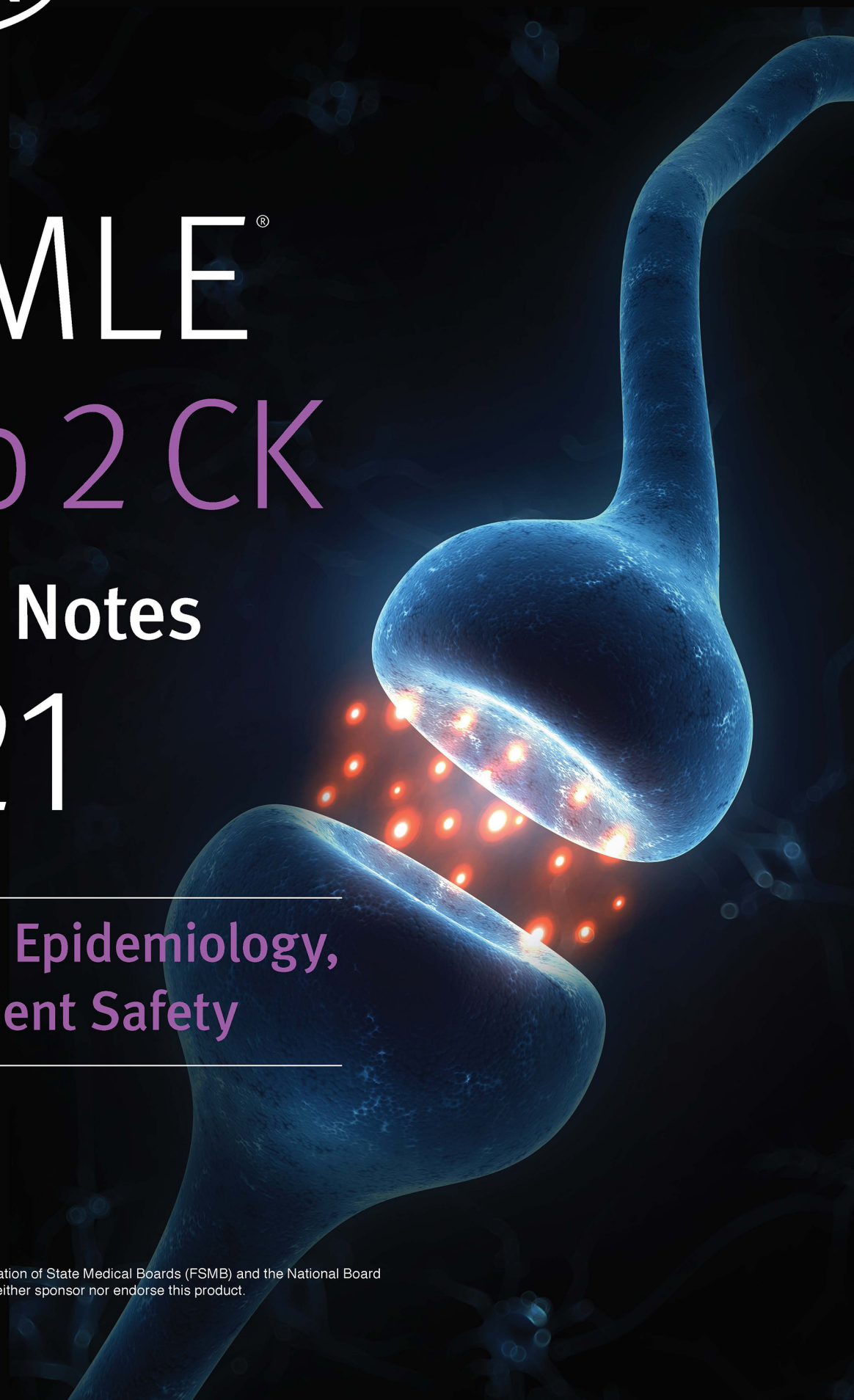

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We want to hear what you think. What do you like or not like about the Notes?
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PART I

Psychiatry

Mental Status Examination 1

Learning Objectives

- ❑ List the steps required to perform a mental status examination

The mental status examination is used to describe the clinician's observations and impressions of the patient during the interview. In conjunction with the history of the patient, it is the best way to make an accurate diagnosis.

General Description

- **Appearance:** grooming, poise, clothes, body type (disheveled, neat, childlike, etc.)
- **Behavior:** quantitative and qualitative aspects of the patient's motor behavior (restless, tics, etc.)
- **Attitude toward the examiner:** (cooperative, frank, and seductive)

Mood and Affect

- **Mood:** emotions perceived by the patient (depressed, anxious, angry, etc.)
- **Affect:** patient's present emotional responsiveness (blunted, flat, labile, etc.)
- **Appropriateness:** in reference to the context of the subject (appropriate or inappropriate)

Speech: physical characteristics of speech (relevant, coherent, fluent, etc.)

Perceptual disturbances: experienced in reference to self or the environment (hallucinations, illusions)

- Hallucinations: false sensory perceptions without a stimulus: **auditory** (psychotic disorders), **visual** (drugs, organic diseases), **tactile** (cocaine intoxication, alcohol withdrawal), **olfactory** (seizures)
- Illusions: sensory misperception with a stimulus

Thought

- **Form of thought:** way in which a person thinks (flight of ideas, loose associations, tangentiality, circumstantiality, etc.)
- **Content of thought:** what the person is actually thinking about (delusions, paranoia, and suicidal ideas)

Sensorium and Cognition

- Alertness and level of consciousness (awake, clouding of consciousness, etc.)
- Orientation: time, place, and person
- Memory: recent, remote, recent past, and immediate retention and recall
- Concentration and attention: serial sevens, ability to spell backwards.
- Capacity to read and write: Ask patient to read a sentence and perform what it says.
- Visuospatial ability: copy a figure
- Abstract thinking: similarities and proverb interpretation
- Fund of information and knowledge: calculating ability, name past presidents

Impulse Control: estimated from history or behavior during the interview

Judgment and Insight: ability to act appropriately and self-reflect

Reliability: physician's impressions of the patient's ability to accurately assess his situation

Interviewing Techniques

Open-Ended Questions: Allow the patient to speak in his own words as much as possible.

"Can you describe your pain?"

Closed-Ended Questions: Ask for specific information without allowing options in answering.

"Are you hearing voices?"

Facilitation: Help the patient continue by providing verbal and nonverbal cues.

"Yes, please continue."

Confrontation: Point something out to the patient.

"You seem very upset today."

Leading: Provide the answer in the question.

"Are the voices telling you to hurt yourself?"

Practice Questions

1. A 20-year-old man presents to your office complaining of auditory hallucinations for approximately 7 months in duration. He reports hearing his father's voice and at times his mother's voice as well. The patient appears distressed by the hallucinations and wants your help. Which of the following would be the most appropriate statement at this time?

   (A) "What do the voices say?"
   (B) "Have you taken medication?"
   (C) "Why do you think you hear voices?"
   (D) "How is your relationship with your parents?"
   (E) "Tell me about the voices."

2. A 30-year-old woman comes to see you after her mother's death approximately 3 weeks ago. Since then she has complained of depressed mood and feelings of helplessness. While in your office, she begins to cry. Which of the following would be the next step in the management of this patient?

   (A) Say, "I will come back when you stop crying."
   (B) Say, "Do you feel guilty about your mother's death?"
   (C) Offer tissue and remain silent
   (D) Say, "Go ahead; it is normal to cry."
   (E) Refer to a psychiatrist for further evaluation

1. **Answer: E.** The ideal interviewing technique is to begin with an open-ended question and conclude with closed-ended questions. Choices A, C, D, and E are all open-ended questions. However, the best open-ended question for this patient and the reason he came to see you is choice E.
2. **Answer: C.** One should always express empathy and then give the patient control. By staying silent and offering a tissue, you are doing just that. Choice E is always incorrect.

Defense Mechanisms 2

Learning Objectives

- ❑ List the types of defense mechanisms and the situations in which they are most likely to occur
- ❑ Describe the most common psychological and intelligence tests and their purpose

Id: Drives (instincts) present at birth. The 2 most important drives are sex and aggression.

Ego: Defense mechanisms, judgment, relationship to reality, object relationships; developed shortly after birth

Superego: Conscience, empathy, and morality are formed during latency period; right vs. wrong

DEFENSE MECHANISMS

Defense mechanisms are the way and means that the **ego** wards off anxiety and controls instinctive urges and unpleasant emotions. They are unconscious (except suppression), discrete, dynamic, and irreversible and may be adaptive or maladaptive.

Types of Defense Mechanisms

Projection: Attributing your own wishes, thoughts, or feelings onto someone else.

"I'm sure my wife is cheating on me."

Denial: Used to avoid becoming aware of some painful aspect of reality.

"I know I do not have cancer."

Splitting: External objects are divided into all good or all bad.

"The morning staff is perfect, the evening staff is terrible."

Blocking: Temporary block in thinking.

"I have known him for years but can never seem to remember his name."

Regression: Return to an earlier stage of development, most immature.

> "Ever since my divorce, my 5-year-old has begun to wet the bed."

Somatization: Psychic derivatives are converted into bodily symptoms.

> "Just thinking of the exam I get butterflies in my stomach."

Introjection: Features of the external world are taken and made part of the self.

> The resident physician dresses like the attending whom he admires.

Displacement: An emotion or drive is shifted to another that resembles the original in some aspect.

> "I had to get rid of the dog since my husband kicked it every time we had an argument."

Repression: An idea or feeling is withheld from consciousness; unconscious forgetting.

> "I do not remember having had a dog."

Intellectualization: Excessive use of intellectual processes to avoid affective expression or experience.

> "It is interesting to note the specific skin lesions which seem to arise as a consequence of my end-stage disease."

Isolation: Separation of an idea from the affect that accompanies it.

> "As she arrived at the station to identify the body, she appeared to show no emotion."

Rationalization: Rational explanations are used to justify unacceptable attitudes, beliefs, or behaviors.

> "I did not pass the test because it was harder this year than ever before."

Reaction formation: An unacceptable impulse is transformed into its opposite; results in the formation of character traits.

> "Listen to him tell his family he was not afraid, when I saw him crying."

Undoing: Acting out the reverse of an unacceptable behavior; consists of an act.

> "I need to wash my hands whenever I have these thoughts."

Acting out: Behavioral or emotional outburst.

> "My 10-year-old started getting into trouble right after his mother and I got divorced."

Humor: Permits the expression of feelings and thoughts without personal discomfort.

> "So," said the 300-pound man, "they expected me to place my head between my legs in the event of a plane crash when the best I could manage was placing my chin on my chest."

Sublimation: Impulse gratification has been achieved, but the aim or object has been changed from unacceptable to acceptable; allows instincts to be channeled. Most mature of the defenses.

Jack the Ripper becomes a surgeon.

Suppression: Conscious forgetting; only conscious defense mechanism.

"I would rather talk about my operation after the party is over."

Dissociation: Splitting off of the brain from conscious awareness.

"I hardly remember getting to the hospital after my husband was hit by a car."

Practice Question

A nurse, working in a hospice, has been ignoring an elderly female patient who has terminal cancer. When asked why she has been ignoring the patient, the nurse replied, "She wants to be left alone." Which of the following defense mechanisms best explains her response?

(A) Rationalization
(B) Isolation of affect
(C) Intellectualization
(D) Projection
(E) Denial

Answer: D. The nurse is projecting her wishes by stating that the patient wants to be left alone, when in reality it is *she* who wants to be left alone. Rationalization (A) is making excuses for your behavior. Had that been the answer, she would have made excuses, such as she's too busy, etc.

TESTS

Intelligence Tests

Intelligence Quotient (IQ) measures academic performance. Mean IQ is 100 (SD = 15).

$$IQ = \frac{MA}{CA} \times 100$$

Adults: Wechsler Adult Intelligence Scale Revised (WAIS-R)

Children: Wechsler Intelligence Scale for Children Revised (WISC-R), Stanford-Binet

Personality Tests

Objective tests use simple stimuli, do not need much clinical experience: Minnesota Multiphasic Personality Inventory (MMPI).

Projective tests use ambiguous stimuli, need clinical experience, not diagnostic: Rorschach test (inkblot), Thematic Apperception Test (TAT), sentence completion tests, family drawings.

Childhood Disorders 3

Learning Objectives

- ❏ Describe the degrees of intellectual disability and expected level of function
- ❏ List the different types of learning disorders
- ❏ Describe the presentation of autism spectrum disorder
- ❏ Describe the diagnosis and treatment of childhood disorders likely to present to a psychiatrist, including attention deficit hyperactivity disorder, childhood conduct disorder, oppositional defiant disorder, childhood anxiety, and Tourette syndrome
- ❏ List the approaches to treating childhood enuresis

INTELLECTUAL DISABILITY (ID)

Definition. Formerly called mental retardation. Significantly subaverage intellectual function (IQ <70), as measured by a variety of IQ tests. Must be accompanied by concurrent impairment in adapting to demands of school, work, social, and other environments. Onset is age <18.

Risk Factors/Etiology. Associated genetic and chromosomal abnormalities include inborn errors of metabolism (e.g., lipidoses, aminoacidurias, glycogen storage diseases) and chromosomal abnormalities (e.g., cri du chat, Down, fragile X syndromes). Associated intrauterine infections include rubella, cytomegalovirus, and other viruses. Intrauterine exposure to toxins and other insults such as alcohol, hypoxia, or malnutrition may be causal. Postnatal causes include exposure to toxins and infection, poor prenatal care, postnatal exposure to heavy metals, physical trauma, and social deprivation.

Presenting Symptoms

- **Prevalence:** 1% of the population. Occurs at a 1.2:1 male-to-female ratio.
- **Mild ID (IQ 50–69):** Attain academic skills to approximately the sixth-grade level, often live independently in the community or with minimal supervision, may have problems with impulse control and self-esteem, and may have associated conduct disorder, substance-related disorder, or attention deficit hyperactivity disorder.
- **Moderate ID (IQ 35–50):** Attain academic skills to second-grade level, may be able to manage activities of daily living, work in sheltered workshops, live in residential community settings; have significant problems conforming to social norms (those with Down syndrome are at high risk for early development of Alzheimer's).
- **Severe (IQ 20–35) and profound ID (IQ <20):** Have little or no speech and very limited abilities to manage self-care; require highly supervised care setting.

Physical Examination. Evidence of underlying disorder or injury

Diagnostic Tests. Amniocentesis: May reveal chromosomal abnormalities associated with ID in high-risk pregnancies (mother age >35).

Treatment. Primary prevention includes genetic counseling, good prenatal care, and safe environments. Treatment of associated general medical conditions may improve overall level of cognitive and adaptive function. Special education techniques may improve ultimate level of function. Behavioral guidance and attention to promoting self-esteem may improve long-term emotional adjustment.

Differential Diagnosis. Includes learning and communication disorders, sensory impairment, autism spectrum disorder, borderline intellectual functioning (IQ 70–100), and environmental deprivation.

LEARNING DISORDERS

Definition. Characterized by learning achievement in specific areas that is substantially below expectations, given the patient's age, intelligence, sensory abilities, and educational experience. Types of learning disorder are reading disorder (most common), mathematics disorder, and disorder of written expression.

Risk Factors/Etiology. Some cases are due to the effects of coexisting general medical conditions such as cerebral palsy on central nervous system (CNS) function. Some general medical conditions and substance-induced conditions are associated with learning disorders, including lead poisoning and fetal alcohol syndrome. Many cases have no obvious etiology.

Presenting Symptoms

- Prevalence: 5% of school-age children
- Onset: usually during elementary school
- Perceptual-motor problems
- Conduct disorder, oppositional defiant disorder, and ADHD
- Poor self-esteem and social immaturity
- School failure and behavioral disturbances

Deficits sometimes persist into adulthood and interfere with occupational function.

Diagnostic Tests. IQ testing and academic achievement tests are the major diagnostic tools.

Treatment. Special education to ensure general learning and maximize skills in the deficient areas is the mainstay of treatment. Counseling of patients and families to improve self-esteem, social behavior, and family functioning is helpful.

Differential Diagnosis. Major rule-outs are environmental deprivation, hearing or vision impairment, and ID.

AUTISM SPECTRUM DISORDERS (ASD)

Definition. A group of disorders characterized by problems with social interaction, behavior, and language

Risk Factors/Etiology. The cause is CNS damage due to known or unknown factors. Sites of CNS damage specifically associated with ASD are unknown. General medical conditions associated with ASD include encephalitis, maternal rubella, PKU, tuberous sclerosis, fragile X syndrome, and perinatal anoxia. There is no obvious etiology in many cases.

Presenting Symptoms

- **Prevalence:** 0.08% of the general population. Occurs at a 5:1 male-to-female ratio.
- **Onset:** before age 3
- **Social symptoms:** lack of peer relationships and a failure to use nonverbal social cues
- **Communication symptoms:** absent or bizarre use of speech
- **Behavioral symptoms:** odd preoccupation with repetitive activities, bizarre mannerisms, and rigid adherence to purposeless ritual
- ID is present in 75% of patients with ASD.
- **Physical findings:** higher incidence of abnormal electroencephalograms (EEGs), seizures, and abnormal brain morphology
- **Course:** Approximately 30% of individuals with ASD become semi-independent in adulthood, but almost all have severe residual disabilities.
- Predictors of a poor outcome are associated ID and failure to develop useful speech.
- Seizures develop by adulthood in 25% of autistic individuals.

Physical Examination. Self-injuries caused by head banging or biting sometimes present.

Treatment. The major treatment is family counseling, special education, and newer antipsychotic medications to control episodes of severe agitation or self-destructive behavior.

Differential Diagnosis. Major rule-outs are ID, hearing impairment, environmental deprivation, selective mutism, and Rett syndrome.

ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)

Definition. Characterized by inattention, hyperactivity, and impulsivity that interfere with social or academic function. Symptoms last for ≥6 months, and onset occurs age <12. Symptoms are present in multiple settings. Subtypes are based on the predominance of symptoms of inattention or of hyperactivity and impulsivity.

Risk Factors/Etiology. No specific etiologies have been identified. Other CNS pathology and disadvantaged family and school situations are sometimes present.

Prevalence. 5% of school-age children and 2.5% of adults. Male-to-female ratio is 2:1 in children and 1.6:1 in adults.

Family history. ADHD, mood and anxiety disorders, substance-related disorders, and antisocial personality disorder

Onset. Usually first recognized when a child enters school, and symptoms usually persist throughout childhood. ADHD, particularly the attention deficit, persists into adulthood in most but not all affected individuals. Hyperactivity tends to diminish in adolescence and adulthood.

Symptoms. Short attention span, constant fidgeting, inability to sit through cartoons or meals, inability to wait in lines, failure to stay quiet or sit still in class, disobedience, shunning by peers, fighting, poor academic performance, carelessness, and poor relationships with siblings

Common Associated Problems. Low self-esteem, mood lability, conduct disorder, learning disorders, clumsiness, communication disorders, drug abuse, school failure, and physical trauma as a result of impulsivity

Physical Examination. Perceptual: motor problems and poor coordination may be present.

Diagnostic Tests. IQ tests and various structured symptom-rating scales for use by teachers and parents are often used.

Differential Diagnosis. Major rule-outs are age-appropriate behavior, response to environmental problems, ID, ASD, and mood disorders.

Treatment. Target symptoms are defined before initiating treatment. Psychological, social, and educational interventions include adding structure and stability to home and school environments. Specialized educational techniques include the use of multiple sensory modalities for teaching, instructions that are short and frequently repeated, immediate reinforcement for learning, and minimization of classroom distractions. Pharmacotherapy of choice is stimulant medications, such as methylphenidate and dextroamphetamine. Non-stimulants such as atomoxetine may also be used. They are usually effective in decreasing hyperactivity, inattention, and impulsivity. Other medications include antidepressants and clonidine.

CONDUCT DISORDER

Definition. Persistent violations ≥6 months in 4 areas: aggression, property destruction, deceitfulness or theft, and rules

Risk Factors/Etiology. Genetic influences play a role by affecting temperament. Stressful family and school environments have also been implicated.

Prevalence. 4% of school-age children. Seen more in males.

Family History. Antisocial personality disorder, conduct disorder, ADHD, mood disorders, and substance-related disorders

Onset. Most often during late childhood or early adolescence. In most individuals, symptoms gradually remit.

Key Symptoms. Bullying, fighting, cruelty to people or animals, rape, vandalism, fire-setting, theft, robbery, running away, school truancy

Complications. Substance-related disorders and school failures

Outcome. Often, antisocial personality disorder, somatic symptom disorders, depressive disorders, and substance-related disorders

Differential Diagnosis. Major rule-outs are environmental problems, ADHD, and oppositional defiant disorder.

Treatment. Healthy group identity and role models are provided by structured sports programs and other programs (e.g., Big Brothers Big Sisters). Structured living settings that place value on group identification and cooperation are useful. Punishment and incarceration are not often effective.

OPPOSITIONAL DEFIANT DISORDER

Definition. Persistent pattern lasting at least 6 months of negativistic, hostile, and defiant behaviors toward adults, including arguments, temper outbursts, vindictiveness, and deliberate annoyance

Risk Factors/Etiology. High reactivity and increased motor behavior are innate features of temperament that may predispose to this disorder. Inconsistent or poor parenting may also contribute.

Prevalence. 3% of school-age children. Male-to-female ratio is 1:1 after puberty but boys > girls before puberty.

Onset. Usually in latency or early adolescence and may start gradually. Onset later in girls.

Associated Problems. Family conflict and school failure, low self-esteem and mood lability, early onset of substance abuse, ADHD and learning disorders

Course. Family conflict often escalates after the onset of symptoms.

Outcome. Conduct disorder may follow.

Treatment. Parents should be advised to spend time interacting with a child, to reward desired behavior and not simply punish undesired behavior, and to be consistent in statements and deeds. Alternative caregivers may be indicated in some cases.

Differential Diagnosis. Conduct disorder

CHILDHOOD ENURESIS

Definition. Characterized by repeated voiding of urine into the patient's clothes or bed in a child age ≥5. It is diagnosed only if the behavior is not due to a medical condition.

Risk Factors/Etiology. Current psychologic stress, family history of enuresis, and urinary tract infections

Prevalence. 3–5% of children aged 10. Slightly more common in boys. May occur only at night, only during daytime, or both. Often causes emotional turmoil in the child or parents.

Physical Examination. Assessment for urinary tract infection or abnormalities should occur.

Treatment. Appropriate toilet training and avoiding large amounts of fluids before bed are important, as are decreasing emotional stressors. A bell-pad apparatus is the best treatment. Pharmacotherapy includes imipramine and desmopressin (DDAVP) for short-term treatment.

CHILDHOOD ANXIETY

Definition. Normal childhood anxiety:

- **Stranger anxiety:** fear of strangers in unfamiliar contexts that is present from age 6 months to approximately 2 years
- **Separation anxiety:** fear of separation from the caregiver that is present from approximately 1 to 3 years of age

Risk Factors/Etiology. Excessively close-knit families, excessive expectations of children, and innate temperamental anxiety

Prevalence. 5% of school-age children

Key Symptoms. Prominent physical complaints such as stomachaches and malaise, unrealistic fears (e.g., monsters) and nightmares, phobias such as school phobia and fear of animals or the dark, difficulty sleeping, and self-mutilation such as scratching, nail-biting, and hair-pulling

Physical Examination. Evidence of nail biting and scratching is sometimes present.

Treatment. Family therapy helps parents recognize and lessen childhood anxiety. Cognitive behavioral therapy is useful to decrease anxiety in older children.

Complications. Social avoidance, low self-esteem, and inhibited social development may occur.

TOURETTE DISORDER

Definition. Childhood onset of multiple motor and vocal tics

Risk Factors/Etiology. Autosomal dominant transmission may occur in some cases. There are associations between ADHD (50%) and obsessive compulsive disorder (OCD) (40%). Abnormalities in the dopaminergic and adrenergic system have been implicated.

Prevalence. 3 per 1,000. More common in males.

Onset. Average age 7 years, with motor tics and vocal tics typically appearing at age 11 years

Course. Vocal and motor tics wax and wane over time.

- **Motor tics** may present as twitching of face, trunk, or extremities or may involve complex behaviors such as pacing, spinning, or touching.
- **Vocal tics** are usually grunts, but coprolalia (cursing) occurs in about 10% of cases.

Associated Problems. ADHD and OCD are each present in about one-third of cases. ADHD occurs before tics whereas OCD symptoms occur after the tics.

Course. Lifelong, with remissions and exacerbations

Treatment. Antipsychotic drugs, including pimozide, haloperidol, olanzapine and risperidone. Clonidine and clonazepam are sometimes useful.

Practice Question

A 13-year-old boy is referred by his school principal for evaluation of his short attention span and inability to sit quietly in class or on the school bus. He has a quick temper at school and at home, and his peers tease him about his temper. Which of the following is most likely to be an associated finding in this case?

(A) Affectual blunting
(B) Autistic mannerisms
(C) Conduct disturbances
(D) Grandiosity and inflated self-esteem
(E) Intellectual disability

Answer: C. The symptoms are suggestive of ADHD. Conduct disturbances are a common associated finding in individuals with ADHD; drug abuse is also more common. Affect tends to be more labile, and low self-esteem is common. Although ID is seen more often in children with ADHD than in the general population, it is not a common associated finding, and this boy is at the expected grade level for his age. ASD is rarely diagnosed in individuals with ADHD.

Depressive, Bipolar, and Related Disorders

4

Learning Objectives

- ❑ List the diagnostic criteria and treatment approaches for major mood disorders, including major depressive, bipolar, cyclothymic, and persistent depressive disorders
- ❑ Describe the presentation of mood disorders related to triggering phenomenon, including seasonal pattern, grief, peri/postpartum, and death/dying

MAJOR DEPRESSIVE DISORDER (MAJOR DEPRESSION)

A 70-year-old woman was recently admitted after her son informed the doctor that she had been doing very poorly over the past few months. The patient reports a 30-pound weight loss, decreased concentration, feelings of helplessness and hopelessness, decreased energy, depressed mood, and decreased sleep.

Definition. Mood disorder that presents with at least a 2-week course of symptoms that is a change from the patient's previous level of functioning. Must have depressed mood or anhedonia (inability to enjoy oneself).

Risk Factors/Epidemiology. Major depression is seen more frequently in women due to several factors, such as hormonal differences, great stress, or simply a bias in the diagnosis. The typical age of onset is age 40. There is also a higher incidence in those who have no close interpersonal relationships or are divorced or separated. Many studies have reported abnormalities in serotonin, norepinephrine, and dopamine. Other risk factors include family history, exposure to stressors, and behavioral reasons, such as learned helplessness.

Presenting Symptoms

- Depressed mood most of the day
- Anhedonia during most of the day
- Significant weight loss (>5% of body weight)
- Insomnia
- Psychomotor agitation or retardation
- Fatigue or loss of energy nearly every day
- Feelings of worthlessness or guilt
- Diminished ability to concentrate
- Recurrent thoughts about death

Physical Examination. Usually within normal limits; however, may find evidence of psychomotor retardation, such as stooped posture, slowing of movements, slowed speech, etc. May also find evidence of cognitive impairment, such as decreased concentration and forgetfulness.

May also include:

- **Psychotic features:** worse prognosis
- **Atypical features:** increased weight, appetite, and sleep

Treatment. Must first secure the safety of the patient, given that suicide is such a high risk. Pharmacotherapy includes antidepressant medications such as SSRIs, tricyclic antidepressants (TCAs), or monoamine oxidase inhibitors (MAOIs). Electroconvulsive therapy (ECT) may be indicated if patient is suicidal or intolerant to medications. Individual psychotherapy is indicated to help the patient deal with conflicts, sense of loss, etc. Another form of therapy is cognitive therapy, which will change the patient's distorted thoughts about self, future, world, etc.

Differential Diagnosis

- **Medical disorders:** hypothyroidism, Parkinson's disease, dementia, medications such as hypertensives, pseudodementia, tumors, cerebrovascular accidents
- **Mental disorders:** other mood disorders, substance disorders, and grief

BIPOLAR I DISORDER

> A 19-year-old college student is taken to the school counselor after he fails several classes. The patient is enrolled in numerous classes, most of which have conflicting times. His grades are poor, yet he seems undisturbed by this. He is also enrolled in numerous organizations such as the chess club, drama club, student government, sports, and at least 2 fraternities. His speech is pressured and he has psychomotor agitation.

Definition. A mood disturbance in which the patient typically experiences symptoms of mania or elevated mood for at least 1 week and that cause significant distress or impairment in level of functioning.

Risk Factors/Epidemiology. Bipolar disorder affects men and women equally and has a mean age of onset of about 18 years. More prevalent among high socioeconomic status. Considered to be the illness with the greatest genetic linkage. Coexisting disorders may include anxiety, alcohol dependence, and substance-related disorders.

Presenting Symptoms

- Abnormal or persistently elevated mood lasting at least 1 week
- Increased self-esteem or grandiosity
- Distractibility flight of ideas
- Excessive involvement in activities, especially goal-directed activities
- More talkative than usual
- Psychomotor agitation
- Increased sexual activity

Physical Examination. Usually within normal limits; however, may find evidence of psychomotor agitation and pressured speech

Treatment. Must assess patient safety to determine the need for hospitalization. Pharmacotherapy will include mood stabilizers, benzodiazepines, and antipsychotics.

Differential Diagnosis

- **Mental disorders:** schizophrenia, personality disorders, and bipolar II disorder (includes major depressive episodes and hypomanic but not manic episodes)
- **Medical disorders:** CNS infections, tumors, hyperthyroidism, and medications

PERSISTENT DEPRESSIVE DISORDER (DYSTHYMIA)

> Mr. Smith complains of poor appetite, low energy, poor concentration, and difficulty in making decisions, which affect his ability to complete his assignments at work. These symptoms have been present for more than 2 years.

Definition. A chronic disorder characterized by a depressed mood that lasts most of the day and is present on most days for at least 2 years

Risk Factors/Epidemiology. Patients typically have other psychiatric disorders, such as anxiety, substance abuse, and/or borderline personality disorders.

Treatment. Hospitalization is usually not indicated. Patients may benefit from psychotherapy to help overcome long-term sense of despair and resolve conflicts from childhood. If medications are indicated, SSRIs, TCAs, or MAOIs are usually preferred.

Differential Diagnosis. Differential diagnosis is essentially the same as for major depression.

CYCLOTHYMIC DISORDER

> Mrs. McDonald has experienced a 12-year history of periods of feeling great followed by periods of feeling lousy. During her feeling-great periods, she experiences increased sexual drive, euphoric mood, and increased irritability. During her feeling-lousy periods, she experiences insomnia, fatigue, and low self-esteem.

Definition. A chronic disorder characterized by many periods of depressed mood and many periods of hypomanic mood for at least 2 years

Risk Factors/Epidemiology. Many patients have interpersonal and marital difficulties. It frequently coexists with borderline personality disorder and is seen more frequently in women. Many patients have family history of bipolar disorder. Alcohol and substance abuse are common.

Treatment. Antimanic drugs such as lithium, carbamazepine, and valproic acid are typically the drugs of choice. Psychotherapy will help patients gain insight into their illness and how to cope with it.

Differential Diagnosis

- **Medical:** seizures, substances, and medications
- **Mental:** other mood disorders, personality disorders, medications

MAJOR DEPRESSIVE DISORDER WITH SEASONAL PATTERN

A young woman from Minnesota complains of depressed mood and sleep disturbances every winter. Her symptoms resolve in the spring and summer.

Definition. A disorder characterized by depressive symptoms found during winter months and absent during summer months. Believed to be caused by abnormal melatonin metabolism (decreased MSH).

Treatment. Phototherapy

GRIEF, POSTPARTUM DEPRESSION, DEATH AND DYING

Grief

Table I-4-1. Grief Versus Depression

Grief or Bereavement	Depression
Sadness, tearfulness, decreased sleep, decreased appetite, decreased interest in the world	Sadness, tearfulness, decreased sleep, decreased appetite, decreased interest in the world
Symptoms wax and wane	Symptoms pervasive and unremitting
Shame and guilt less common	Shame and guilt are common
Threaten suicide less often	Threaten suicide more often
Symptoms can last up to 1 year	Symptoms continue for more than 1 year
Usually return to baseline level of functioning within 2 months	Patients do not return to baseline level of functioning
Treatment includes supportive psychotherapy	Treatment includes antidepressant medication

Peripartum Mood Disorders

Table I-4-2. Postpartum Reactions

Onset	Disorder	Symptoms	Mother's Feelings Toward Baby	Treatment
Onset of mood symptoms within 2 wks after delivery	Postpartum blues or baby blues	Sadness, mood lability, tearfulness	No negative feelings	Supportive, usually self-limited
Onset of mood symptoms occurs during pregnancy or in the 4 wks following delivery	Depressive disorder with peripartum onset	Depressed mood, weight changes, sleep disturbances, and excessive anxiety	May have negative feelings toward baby	Antidepressant medication
Onset of mood and/or psychotic symptoms occurs during pregnancy or in the 4 wks following delivery	Bipolar disorder with peripartum onset Brief psychotic disorder with peripartum onset	Symptoms of depression, mania along with delusions, hallucinations, and thoughts of harm	May have thoughts of harming baby	Antipsychotic medication, lithium, and possible antidepressant

Death and Dying

Through her work with dying hospital patients, psychiatrist Elizabeth Kubler-Ross identified 5 stages she believed were experienced by those nearing death. The stages do not have to occur in order.

Stage 1: Shock and denial
Stage 2: Anger
Stage 3: Bargaining
Stage 4: Depression
Stage 5: Acceptance

Practice Questions

1. A 50-year-old woman is taken to the hospital after neighbors find her wandering the streets mumbling to herself and gesturing. When approached, she begins to cry and expresses thoughts about hurting herself. Examination reveals scratch marks on both her forearms and questionable lacerations on her throat. When questioned, she reports feeling depressed since her husband died 5 months ago. She reports a decrease in concentration and feelings of helplessness, hopelessness, and anhedonia, which resulted in her quitting her job and staying at home. She now has begun to hear her husband's voice asking her to "join" him. Which of the following would be the next step in management?

   (A) Begin a trial of antidepressant medications
   (B) Refer to psychiatry
   (C) Refer for electroconvulsive therapy
   (D) Assess for thoughts about suicide
   (E) Refer to the outpatient department for follow-up

2. Assuming you decide to begin treatment, which of the following is most indicated as initial treatment?

   (A) Individual psychotherapy
   (B) Behavioral therapy
   (C) Fluoxetine
   (D) Risperidone
   (E) Phenelzine

3. A 32-year-old woman was recently diagnosed with advanced breast cancer. Which of the following reactions would you expect to see first?

   (A) Shock and denial
   (B) Anger
   (C) Bargaining
   (D) Depression
   (E) Any of the above

1. **Answer: D.** The most important thing to assess in patients suffering from depression is their suicidal status, which of course determines her prognosis and whether or not you will admit her to the hospital for treatment. You will probably begin a course of pharmacotherapy, but you need to assess suicidal status first. "Refer to psychiatry" will always be wrong on a test, given that you need to know what to do in these situations. Electroconvulsive therapy might be indicated in her condition but is usually not the first line of treatment.
2. **Answer: D.** Patients with both mood and psychotic symptoms respond to both antidepressants as well as to antipsychotic medication. However, you must treat the worst symptom first. In this case, the antipsychotic would be most indicated to reduce her psychotic symptoms. Choice D is an atypical antipsychotic medication with minimal side effects.
3. **Answer: E.** Because the stages can occur in any order, any one of the above could be the answer.

Schizophrenia and Other Psychotic Disorders

5

Learning Objectives

- ❑ List the diagnostic criteria and treatment approaches to schizophrenia and other psychotic disorders

SCHIZOPHRENIA

Definition. A thought disorder that impairs judgment, behavior, and ability to interpret reality. Symptoms must be present for at least 6 months to be able to make a diagnosis.

Risk Factors/Etiology. Men have an earlier onset, usually at age 15–25. Many theories have evolved regarding the cause of schizophrenia.

- Schizophrenia has been associated with high levels of dopamine and abnormalities in serotonin.
- Because there is an increase in the number of schizophrenics born in the winter and early spring, many believe it may be viral in origin.

Schizophrenia is more prevalent in low socioeconomic status groups, either as a result of downward drift or social causation.

Prevalence

General population..... 1%	One schizophrenic parent.....12%
Monozygotic twin..... 47%	Two schizophrenic parents 40%
Dizygotic twin..... 12%	First-degree relative.....12%
	Second-degree relative 5–6%

Physical and Psychiatric Presenting Symptoms

- Hallucinations (mostly auditory)
- Delusions (mostly bizarre)
- Disorganized speech or behavior
- Catatonic behavior
- Negative symptoms
- Social and/or occupational dysfunction
- Physical exam usually unremarkable, but may find saccadic eye movements, hypervigilance, etc.

Brain Imaging Findings

- **CT:** lateral and third **ventricular enlargement**, **reduction in cortical volume** (associated with the presence of negative symptoms, neuropsychiatric impairment, increased neurologic signs, and poor premorbid adjustment)
- **MRI:** increased cerebral ventricles
- **PET:** hypoactivity of the frontal lobes and hyperactivity of the basal ganglia relative to the cerebral cortex

Psychologic Tests

- **IQ tests:** Will score lower on all IQ tests, maybe due to low intelligence at the onset or to deterioration as a result of the disease.
- **Neuropsychologic:** Tests usually are consistent with bilateral frontal and temporal lobe dysfunction, including deficits in attention, retention time, and problem-solving ability.
- **Personality:** May give abnormal findings, such as bizarre ideations, etc.

Treatment. Hospitalization is usually recommended for either stabilization or safety of the patient. If you decide to use medications, antipsychotic medications are most indicated to help control both positive and negative symptoms. If no response, consider using clozapine after other medications have failed. The suggested psychotherapy will be supportive psychotherapy with the primary aim of having the patient understand that the therapist is trustworthy and has an understanding of the patient, no matter how bizarre.

Differential Diagnosis

- **Substance-induced:** Psychostimulants, hallucinogens, alcohol hallucinosis, barbiturate withdrawal, etc. Consider urine drug screen to rule out.
- **Epilepsy:** temporal lobe epilepsy
- **Other psychotic disorders:** schizoaffective, schizophreniform, brief reactive psychosis, delusional disorder
- **Malingering and factitious disorder:** Must assess whether the patient is in control of the symptoms and whether there is an obvious gain.
- **Mood disorders:** Look at duration of mood symptoms; these tend to be brief in schizophrenia.
- **Medical:** HIV, steroids, tumors, CVAs, etc. Need medical work-up to rule out.
- **Personality disorders:** Schizotypal, schizoid, and borderline personality disorders have the most similar symptoms. Must look at duration of symptoms as well as patient's level of functioning.

OTHER PSYCHOTIC DISORDERS

Brief Psychotic Disorder

A 35-year-old female Chinese immigrant is brought in by neighbors after she was found wandering in the streets yelling out someone's name. She appears disheveled and grossly disorganized. You learn that she arrived in the U.S. several days ago, and upon her arrival witnessed the death of her 3-year-old son. While in the waiting room, she appears to be responding to internal stimuli. Her symptoms of psychosis resolve fully within 1 month.

Presenting Symptoms

- Hallucinations
- Delusions
- Disorganized speech
- Grossly disorganized or catatonic behavior
- Symptoms more than 1 day but less than 30 days

Risk Factors. Seen most frequently in the low socioeconomic status as well as in those who have preexisting personality disorders or the presence of psychological stressors.

Treatment. Hospitalization is warranted if the patient is acutely psychotic, to assure the safety of her/himself or of others. Pharmacotherapy will include both antipsychotics and benzodiazepines. The benzodiazepines may be used for short-term treatment of psychotic symptoms.

Schizophreniform Disorder

> Mrs. Jones is evaluated at a nearby clinic after she was noticed to be acting inappropriately at work. According to her coworkers, she began acting strangely 3 months ago. At that time she began wearing a hard hat to work and when asked why, replied, "I will not let you read my mind." She also believed that others were talking about her and routinely asked them to stop. On several occasions, she had to be escorted out of the room because she started to argue with others whom she believed were controlling her mind.

Presenting Symptoms

- Hallucinations
- Delusions
- Disorganized speech
- Grossly disorganized or catatonic behavior
- Negative symptoms
- Social and/or occupational dysfunction
- Symptoms are present more than 1 month but less than 6 months
- Most of the patients return to their baseline level of functioning

Risk Factors. Suicide is a risk factor given that the patient is likely to have a depressive episode after the psychotic symptoms resolve.

Treatment. Must assess whether the patient needs hospitalization, to assure safety of patient and/or others.

Antipsychotic medication is indicated for a 3–6-month course. Individual psychotherapy may be indicated to help the patient assimilate the psychotic experience into his life.

Schizoaffective Disorder

A 25-year-old woman is found walking nude in the shopping mall. When asked why, she replies, "I am making it easy for others to have sex with me since I know they all want me." She states she heard a voice telling her she was irresistible and everyone wanted her. When she speaks, she cannot focus on one topic at a time. Her mood is euphoric and her affect labile. She recounts an episode last year where, although she did not have an elevated or depressed mood, she heard voices she could not describe and believed others were following her. These symptoms lasted for 6+ months and caused her to lose her job.

Presenting Symptoms

- Uninterrupted period of symptoms meeting criteria for major depressive episode, manic episode, or mixed episode
- Symptoms for schizophrenia
- Delusions or hallucinations for at least 2 weeks in the absence of mood symptoms

Prognosis. Better prognosis than patients with schizophrenia. Worse prognosis than patients with affective disorders.

Treatment. First determine if hospitalization is necessary. Use antidepressant medications and/or anticonvulsants to control the mood symptoms. If not effective, consider antipsychotics to help control the ongoing symptoms.

Delusional Disorder

Mr. Smith has been married for 10 years, and during most of those years he believed his wife was trying to poison him to get his money. He frequently complains of stomach pain, which he believes is due to the poison in the food. His thoughts are logical and coherent. He denies any hallucinations. His wife, an independently wealthy woman, does not understand her husband's logic because she has more money than he does.

Presenting Symptoms

- Nonbizarre delusions for at least 1 month
- No impairment in level of functioning
- The patients are usually reliable unless it is in relationship to their delusions.
- Types include erotomanic, jealous, grandiose, somatic, mixed, unspecified.

Risk Factors. Mean age of onset is about age 40. Seen more commonly in women, and most are married and employed. Has been associated with low socioeconomic status as well as recent immigration. Can usually see conditions in limbic system or basal ganglia, if medical causes are determined to be the cause of the delusions.

Treatment. Outpatient treatment is usually preferred, but the patient may need hospitalization while you rule out medical causes. Pharmacotherapy consists of antipsychotic medications, but studies indicate that many patients do not respond to treatment. Individual psychotherapy is recommended, having the patient trust the physician to point out how the delusions interfere with normal life.

Practice Questions

1. A 23-year-old woman was seen today after she complained that her neighbors were talking about her. According to the neighbors, her behavior started 3 weeks ago after she was involved in a car accident. She was not injured in the accident. Since then, she has been following the neighbors for several days and harassing them at work. She believes that the neighbors are putting poison in her food and want to kill her. When asked why, she is unable to give a clear explanation but insists that what she is saying is true. She states that the voice in her head told her it is true and that you should stop asking questions. While in the waiting room, you observe her to be dressed bizarrely and laughing inappropriately. Which of the following is most indicated in management?

   (A) Haloperidol
   (B) Clozapine
   (C) Lorazepam
   (D) Risperidone
   (E) Fluphenazine decanoate

2. If her symptoms do not improve within the next week, which of the following is she at greatest risk of developing?

   (A) Schizophrenia, paranoid type
   (B) Schizoaffective disorder
   (C) Schizophreniform disorder
   (D) Schizotypal personality disorder
   (E) Delusional disorder

1. **Answer: D.** The patient clearly has psychotic symptoms; therefore, you would want to give her medication with the fewest side effects. Choices A and E are typical antipsychotics with many side effects. Choices B and D are atypical antipsychotics; however, clozapine is not used first line in the treatment of psychotic symptoms. Lorazepam is not an antipsychotic medication. However, it can be used in psychotic patients to reduce agitation.
2. **Answer: C.** Because her symptoms have occurred for only 3 weeks, this patient has a diagnosis of brief psychotic disorder. But should the symptoms persist for >1 month, her diagnosis would be schizophreniform disorder. Schizophrenia is given when the symptoms are present for >6 months.

Anxiety Disorders 6

Learning Objectives

- ❑ Describe the presentation, diagnostic criteria, and treatment approaches to anxiety disorders, including panic, phobic, obsessive-compulsive, acute stress, post-traumatic stress, and generalized anxiety disorders

ANXIETY

Anxiety is a syndrome with psychologic and physiologic components. **Psychologic** components include worry that is difficult to control, hypervigilance and restlessness, difficulty concentrating, and sleep disturbance. **Physiologic** components include autonomic hyperactivity and motor tension.

Psychodynamic theory posits that anxiety occurs when instinctual drives are thwarted. **Behavioral theory** states that anxiety is a conditioned response to environmental stimuli originally paired with a feared situation. **Biologic theories** implicate various neurotransmitters (especially gamma-aminobutyric acid [GABA], norepinephrine, and serotonin) and various CNS structures (especially reticular activating system and limbic system).

PANIC DISORDER

Definition. Recurrent, unexpected panic attacks that take place out of the blue. Panic attacks are attacks of intense anxiety that often include marked physical symptoms, such as tachycardia, hyperventilation, dizziness, and sweating. Attacks involve worry about having more attacks.

Risk Factors/Etiology. History associated with panic disorder includes separations during childhood and interpersonal loss in adulthood. A majority of individuals with panic disorder, unlike other individuals, have panic symptoms in response to "panicogens" (lactate CO_2, yohimbine, caffeine, and other substances). Studies of twins suggest a genetic component.

Presenting Symptoms

- **Prevalence:** 2% of the population; women > men 2:1
- **Onset:** often during decade 3
- **Course:** Severity of symptoms may wax and wane, and may be associated with intercurrent stressors.
- **Key symptoms:** Attacks usually last a few minutes.

- **Associated problems:** depression, generalized anxiety, and substance abuse
- **Agoraphobia** is fear or avoidance of places from which escape would be difficult in the event of panic symptoms (public places, being outside alone, public transportation, crowds). Women > men. Often leads to severe restrictions on the individual's travel and daily routine.

Treatment. Pharmacologic interventions include SSRIs, alprazolam, clonazepam, imipramine, and MAOIs (e.g., phenelzine). Psychotherapeutic interventions include relaxation training for panic attacks and systematic desensitization for agoraphobic symptoms.

PHOBIC DISORDERS

Phobic disorders are characterized by an irrational fear and avoidance of objects and situations.

Types of Phobias

- **Specific phobia:** Fear or avoidance of objects or situations other than agoraphobia or social phobia. Commonly involves animals (e.g., carnivores, spiders), natural environments (e.g., storms), injury (e.g., injections, blood), and situations (e.g., heights, darkness).
- **Social anxiety disorder:** Fear of humiliation or embarrassment in either general or specific social situations (e.g., public speaking, "stage fright," urinating in public restrooms).

Treatment. Cognitive-behavioral therapies for phobias include systematic desensitization and assertiveness training. Pharmacotherapy includes SSRIs, buspirone, and beta-blockers (for stage fright).

OBSESSIVE-COMPULSIVE DISORDER (OCD)

Definition. OCD is characterized by recurrent obsessions or compulsions that are recognized by the individual as unreasonable. Obsessions are anxiety-provoking, intrusive thoughts commonly concerning contamination, doubt, guilt, aggression, and sex. Compulsions are peculiar behaviors that reduce anxiety, commonly hand-washing, organizing, checking, counting, and praying.

Risk Factors/Etiology. May be associated with abnormalities of serotonin metabolism

Presenting Symptoms

- **Prevalence:** 2% of population; men = women 1:1
- Some evidence of heritability
- **Onset:** insidious and occurs during childhood, adolescence, or early adulthood
- **Course:** Symptoms usually wax and wane, and depression, other anxieties, and substance abuse are common.

Physical Examination. Chapped hands when handwashing compulsion is present.

Treatment. Behavioral psychotherapies are relaxation training, guided imagery, exposure, paradoxical intent, response prevention, thought-stopping techniques, and modeling. Pharmacotherapy includes SSRIs, TCAs, MAOIs, and SNRIs.

ACUTE STRESS DISORDER/POST-TRAUMATIC STRESS DISORDER

Definition. These disorders are characterized by severe anxiety symptoms and follow a threatening event that caused feelings of fear, helplessness, or horror.

- When the anxiety lasts <1 month (but >2 days) and symptoms occur within 1 month of stressor, it is diagnosed as **acute stress disorder** (**ASD**).
- When the anxiety lasts >1 month, it is diagnosed as **post traumatic stress disorder** (**PTSD**).

Risk Factors/Etiology. Traumatic events precipitate ASD and PTSD. Premorbid factors, such as personality traits, play an uncertain role.

Presenting Symptoms

- May occur at any age. About 50% of cases resolve within 3 months.
- Usually begin immediately after trauma, but may occur after months or years.
- Three key symptom groups
  - Reexperiencing of traumatic event: dreams, flashbacks, or intrusive recollections
  - Avoidance of stimuli associated with the trauma or numbing of general responsiveness
  - Increased arousal: anxiety, sleep disturbances, hypervigilance
- Anxiety, depression, impulsivity, and emotional lability are common.
- **"Survivor guilt"**: A feeling of irrational guilt about an event sometimes occurs.

Treatment. Counseling after a stressful event may prevent PTSD from developing. Group psychotherapy with other survivors is helpful. Pharmacotherapy includes SSRIs, other antidepressants, and benzodiazepines. Prazosin has been used to reduce nightmares.

GENERALIZED ANXIETY DISORDER

Definition. Excessive, poorly controlled anxiety about life circumstances that continues for >6 months. Both psychologic and physiologic symptoms of anxiety are present. General worry is accompanied by somatic symptoms such as irritability, decreased sleep, and poor concentration.

Risk Factors/Etiology. May be a genetic predisposition for an anxiety trait.

Presenting Symptoms

- **Prevalence:** 5% of the population. Occurs at a 2:3 male-to-female ratio.
- **Onset:** often during childhood but can occur later
- **Course:** usually chronic, but symptoms worsen with stress
- **Associated problems:** depression, somatic symptoms, and substance abuse

Treatment. Behavioral psychotherapy includes relaxation training and biofeedback. Pharmacotherapy includes SSRIs, venlafaxine, buspirone, and benzodiazepines.

Practice Question

A 31-year-old local politician has a sudden onset of extreme anxiety, tremulousness, and diaphoresis immediately before his first scheduled appearance on national television, and he is unable to go on the air. For the next week he is paralyzed by fear each time he faces an audience, and he cancels all of his scheduled public appearances. Which of the following is the most likely diagnosis?

(A) Acute stress disorder
(B) Adjustment disorder with anxious mood
(C) Panic disorder
(D) Social anxiety disorder
(E) Specific phobia

Answer: D. This presentation is most suggestive of social anxiety disorder. In this case, exposure to public speaking precipitated intense anxiety. Panic disorder is also characterized by intense anxiety attacks; however, there is no clear precipitant. Specific phobia, situational type, is a less likely diagnosis, because there is no specific cause of the fear other than social exposure. Acute stress disorder is characterized by the presence of intrusive recollections and emotional numbing that follow a life-threatening event. Adjustment disorder with anxious mood is characterized by an adaptation problem that follows a psychologic stressor, of which there is no evidence in this case.

Somatic Symptom and Related Disorders

7

Learning Objectives

- ❑ Differentiate conversion disorder, factitious disorder, and malingering
- ❑ Answer questions about somatic symptom, illness anxiety, and body dysmorphic disorders

SOMATOFORM DISORDERS

Somatoform disorders are characterized by the presentation of physical symptoms with no medical explanation. The symptoms are severe enough to interfere with one's ability to function in social or occupational activities.

SOMATIC SYMPTOM DISORDER

> Mrs. Smith has been married for 10 years, and during all of those years she remembers being sick all of the time. According to her husband, she constantly takes medications for all of her ailments. She has visited numerous physicians and none have been able to correctly diagnose her condition. Today she presents in your office complaining of shortness of breath, chest pain, abdominal pain, back pain, double vision, difficulty walking due to weakness in her legs, headaches, constipation, bloating, decreased libido, and tingling in her fingers.

Definition. A disorder where 1 or more somatic symptoms that are distressing result in problems in functioning.

Risk Factors/Etiology. Somatization disorder affects women more than men and is usually inversely related to SES. Usually begins by the age of 30. Data suggest that there may be a genetic linkage to the disorder. Within families, male relatives tend to have antisocial personality disorder, whereas female relatives tend to have histrionic personality disorder.

Physical and Psychiatric Presenting Symptoms

- Many physical symptoms affecting many organ systems
- Excessive thoughts, feelings, or behaviors related to the somatic symptoms
- Long, complicated medical histories

- Interpersonal and psychologic problems are usually present.
- Patients will usually seek out treatment and have significant impairment in their level of functioning.
- Commonly associated with major depressive disorder, personality disorders, substance-related disorders, generalized anxiety disorders, and phobias

Treatment. Must have a single identified physician as the primary caretaker. Patient should be seen during regularly scheduled brief monthly visits. Should increase the patient's awareness of the possibility that the symptoms are psychological in nature. Individual psychotherapy is needed to help patients cope with their symptoms and develop other ways of expressing their feelings.

Differential Diagnosis

- **Medical:** MS, myasthenia gravis, SLE, AIDS, thyroid disorders, and chronic systemic infections
- **Psychiatric:** major depression, generalized anxiety disorder, schizophrenia

CONVERSION DISORDER

A recently married woman presents to the emergency department unable to move her lower extremities. A full workup is done, and no abnormalities are found. When further questioned, she reports being beaten by her husband that morning.

Definition. A disorder in which the individual experiences 1 or more neurologic symptoms that cannot be explained by any medical or neurologic disorder.

Risk Factors/Etiology. Seen more frequently in young women. Also more common among the lower SES, rural populations, low IQs, and military personnel. Commonly associated with passive-aggressive, dependent, antisocial, and histrionic personality disorder.

Psychiatric and Physical Presenting Symptoms

- 1 or 2 neurologic symptoms affecting voluntary or sensory function
- Must have psychologic factors associated with the onset or exacerbation of the symptoms
- Mutism, blindness, and paralysis are the most common symptoms.
- **Sensory system:** anesthesia and paresthesia
- **Motor system:** abnormal movements, gait disturbance, weakness, paralysis, tics, jerks, etc.
- **Seizure system:** pseudoseizures
- **Primary gain:** keeps internal conflicts outside patient's awareness
- **Secondary gain:** benefits received from being "sick"
- **La belle indifference:** Patient seems unconcerned about impairment.
- **Identification:** Patients usually model their behavior on someone who is important to them.

Treatment. Psychotherapy to establish a caring relationship with treater and focus on stress and coping skills. Brief monthly visits with partial physical examinations.

Differential Diagnosis

- **Neurologic:** dementia, tumors, basal ganglia disease, and optic neuritis
- **Psychiatric:** schizophrenia, depressive disorders, anxiety disorders, factitious
- **Other:** malingering

ILLNESS ANXIETY DISORDER

A 22-year-old woman presents to the doctor convinced that she has a brain tumor. She reports frequent headaches that are not alleviated with aspirin. She has been to numerous physicians and all have told her that there is nothing wrong with her. She expects that you can help her because she knows that there is something wrong and that you can adequately treat her condition.

Definition. A disorder characterized by the patient's belief that he/she has some specific disease. Despite constant reassurance, the patient's belief remains the same. Symptoms must occur for >6 months.

Risk Factors/Etiology. Men and women are affected equally. Most common onset is age 20–30.

Physical and Psychiatric Presenting Symptoms

- Preoccupation with diseases
- The preoccupation persists despite constant reassurance by physicians.
- The belief is not delusional.
- The preoccupation affects the individual's level of functioning.
- Duration at least 6 months

Treatment. Psychotherapy to help relieve stress and help cope with illness. Frequent, regularly scheduled visits to patient's medical doctor(s).

BODY DYSMORPHIC DISORDER

The mother of a 20-year-old man presents to your office in tears. She insists that you come to her house and see her son, who has been homebound for several years. Her son refuses to leave the house because he believes he is ugly and people will laugh at him. He feels deformed and refuses to let others see him. When you arrive at the house, you find an attractive young man with no observable deformities.

Definition. Characterized by the belief that some body part is abnormal, defective, or misshapen.

Risk Factors/Etiology. Affects women more than men, typically ages 15–20. These women are unlikely to be married. Other disorders that may be found include depressive disorders, anxiety disorders, and psychotic disorders. Family history of depressive disorders and OCDs. May involve serotonergic systems.

Physical and Psychiatric Presenting Symptoms

- Most common concerns involve facial flaws
- Constant mirror-checking
- Attempt to hide the alleged deformity
- Housebound
- Avoids social situations
- Causes impairment in their level of functioning

Treatment. Individual psychotherapy to help deal with stress of alleged imperfections as well as reality testing. Pharmacotherapy may include the use of SSRIs, TCAs, or MAOIs.

Differential Diagnosis

- **Medical:** some types of brain damage, such as neglect syndrome
- **Psychiatric:** anorexia, narcissistic personality disorder, OCD, schizophrenia, delusional disorder

FACTITIOUS DISORDER

A 2-year-old girl was hospitalized after her mother complained that the girl had multiple episodes of apnea in the middle of the night. The mother was given an apnea monitor to take home and when she returned, there were numerous episodes registering on the monitor. While in the hospital, the girl had no episodes of apnea. However, shortly after her mother's visit, there were numerous episodes recorded on the monitor.

Definition. A disorder characterized by the conscious production of signs and symptoms of both medical and mental disorders. The main objective is to assume the sick role and eventually hospitalization. Usually diagnosed with physical or psychological symptoms or both. Consists of 2 main types: **imposed on self** and **imposed on others**.

Etiology. Seen more commonly in women and in hospital and health care workers. As children, many of the patients suffered abuse that resulted in frequent hospitalizations, thus their need to assume the sick role.

Physical and Psychiatric Presenting Symptoms

- Typically demand treatment when in the hospital
- If tests return negative, they tend to accuse doctors and threaten litigation.
- Become angry when confronted

Treatment. Usually involves management rather than cure. Must be aware of countertransference when the physician suspects factitious disorder.

Differential Diagnosis. Psychiatric: other somatoform disorders, antisocial personality disorder, histrionic personality disorder, schizophrenia, substance abuse, malingering, and Ganser syndrome

MALINGERING

A 40-year-old homeless man presents to the hospital on a cold night complaining of auditory hallucinations telling him to kill himself. When asked about past psychiatric history, he is unable to give any detailed information. He seems concerned about being admitted immediately and refuses all medications when offered.

Definition. Characterized by the conscious production of signs and symptoms for an obvious gain (money, avoidance of work, free bed and board, etc.). It is not a mental disorder.

Risk Factors/Etiology. Seen more frequently in men, especially in prisons, factories, the military, etc.

Physical and Psychiatric Presenting Symptoms

- Most express subjective symptoms
- Tend to complain a lot and exaggerate its effect on their functioning and lives
- Preoccupied more with rewards than with alleviation of symptoms

Treatment. Allow the patient to save face by not confronting the patient and by allowing the physician–patient relationship to work. If confronted, patient will become angry and more guarded and suspicious.

Differential Diagnosis. Psychiatric: somatoform disorders

Practice Question

A 40-year-old woman presents to your office and demands to be seen immediately. She schedules appointments to see you on a regular basis as well as irregularly. She routinely goes to the emergency department when she knows you are at the hospital. She calls your service every night and demands that you call her at home. Her frequent complaints include headache, shortness of breath, double vision, burning at urination, weakness in her arms and legs, tingling in her fingers, and palpitations. All of her medical workups have been negative so far. Which of the following would be the next step in management?

(A) Tell her it is all in her head
(B) Assure her there is nothing wrong with her
(C) Refer her to a psychiatrist
(D) Begin a trial of lorazepam
(E) Schedule regular office visits

Answer: E. Patients with somatic symptom disorder should have only 1 physician, and that physician must see the patient on a regular basis given that there might be something physically wrong in the future. Also, by limiting the patient's care to one physician, the likelihood of unnecessary tests and treatment is reduced.

Neurocognitive Disorders 8

Learning Objectives

- ❑ Differentiate delirium, dementia, and psychosis
- ❑ List the causes of delirium and describe the diagnostic work-up
- ❑ Define neurocognitive disorder and mild neurocognitive disorder

NEUROCOGNITIVE DISORDERS

Cognition includes memory, language, orientation, judgment, problem solving, interpersonal relationships, and performance of actions. Cognitive disorders have problems in these areas as well as behavioral symptoms.

Definition. Characterized by the syndromes of delirium, neurocognitive disorder, and amnesia, which are caused by general medical conditions, substances, or both

Risk Factors/Etiology. Very young or advanced age, debilitation, presence of specific general medical conditions, sustained or excessive exposure to a variety of substances

Presenting Symptoms (Key Symptoms)

- Memory impairment, especially recent memory
- **Aphasia:** failure of language function
- **Apraxia:** failure of ability to execute complex motor behaviors
- **Agnosia:** failure to recognize or identify people or objects
- **Disturbances in executive function:** impairment in the ability to think abstractly and plan such activities as organizing, shopping, and maintaining a home

DELIRIUM

Delirium is characterized by prominent disturbances in alertness, as well as confusion and a short, fluctuating course. It is caused by acute metabolic problems or substance intoxication.

Risk Factors/Etiology. Commonly associated with general medical conditions such as systemic infections, metabolic disorders, hepatic/renal diseases, seizures, head trauma. Also associated with high, sustained, or rapidly decreasing levels of many drugs, especially in the elderly and severely ill.

Presenting Symptoms. Delirium occurs in >40% of elderly, hospitalized patients. Key symptoms include agitation or stupor, fear, emotional lability, hallucinations, delusions, and disturbed psychomotor activity.

Physical Examination. Motor abnormalities commonly present, include incoordination, tremor, asterixis, and nystagmus. Incontinence is common. There is often evidence of underlying general medical conditions or substance-specific syndromes.

Diagnostic Tests. EEG often shows generalized slowing of activity, fast-wave activity, or focal abnormalities. Abnormal findings from neuroimaging and neuropsychiatric testing may be present.

Treatment. Correction of physiologic problems is essential. Frequent orientation and reassurance are helpful. Consider protective use of physical restraints and antipsychotic medications.

Differential Diagnosis. Neurocognitive disorder, substance intoxication or withdrawal, and psychotic disorders are the major rule-outs.

NEUROCOGNITIVE DISORDER

Neurocognitive disorder is characterized by slight (mild) or prominent (severe) memory disturbances coupled with other cognitive disturbances that are present even in the absence of delirium. It is caused by CNS damage and likely to have a protracted course.

Risk Factors/Etiology

- Neurodegenerative disease such as Alzheimer's, Parkinson, Huntington, Pick and other fronto-temporal degeneration, and Creutzfeldt-Jakob disease are common causes.
- Cerebrovascular disease, intracranial processes such as CNS infections (e.g., HIV), traumatic brain injuries, radiation, and/or tumors should be considered.
- Seizure disorders, metabolic disorders (e.g., disease of protein, lipid, and carbohydrate metabolism; diseases of myelin; Wilson disease; uremic encephalopathy), and endocrinopathies (e.g., hypothyroidism) are often associated with neurocognitive disorder.
- Nutritional deficiencies, including beriberi (thiamine [vitamin B1] deficiency), pellagra (niacin deficiency), and/or pernicious anemia (cobalamin [vitamin B12] deficiency) should be considered.
- Toxins that cause neurocognitive disorder include alcohol, inhalants, sedative–hypnotics, anxiolytics, anticonvulsants, antineoplastic medications, heavy metals, insecticides, and solvents.

Prevalence. 5% of the population age >65 and >20% of the population age >85

Heritability. Some types of neurodegenerative neurocognitive disorders (e.g., Huntington disease)

Key Symptoms. Increasing disorientation, anxiety, depression, emotional lability, personality disturbances, hallucinations, and delusions

Associated Findings. Abnormal findings from neuroimaging and neuropsychiatric testing

Course. Depending on the etiology, function may stabilize or deteriorate further.

Physical Examination. Evidence of CNS motor pathology is often present. There may be evidence of underlying general medical conditions or substance-specific syndromes.

Diagnostic Tests. EEG may show specific focal abnormalities. Neuroimaging and neuropsychiatric testing may show specific abnormal findings. Folstein Mini-Mental Status Exam is used to detect neurocognitive disorder. Basic laboratory examination for neurocognitive disorder includes B12 and folate levels, RPR, CBC with SMA, and thyroid function tests.

Treatment. Correction or amelioration of underlying pathology is essential. Medication that further impairs cognition should be avoided. Provision of familiar surroundings, reassurance, and emotional support is often helpful.

Differential Diagnosis. Delirium and less severe, age-related cognitive decline must be ruled out.

Specific Neurocognitive Disorders

All neurocognitive disorders may be mild or severe.

Neurocognitive disorder due to Alzheimer's disease

- Occupy more than 50% of nursing home beds
- Found in 50–60% of patients with neurocognitive disorder
- Risk factors: female, family history, head trauma, Down syndrome
- Neuroanatomic findings: cortical atrophy, flattened sulci, and enlarged ventricles
- Histopathology: senile plaques (amyloid deposits), neurofibrillary tangles, neuronal loss, synaptic loss, and granulovacuolar degeneration of neurons
- Associated with chromosome #21 (gene for the amyloid precursor protein)
- Decreased Ach and NE
- Deterioration is generally gradual; average duration from onset to death is ~8 years.
- Focal neurologic symptoms are rare.
- Treatment includes long-acting cholinesterase inhibitors such as donepezil, rivastigmine, galantamine, and memantine.
- Antipsychotic medications may be helpful when psychotic symptoms present but contraindicated to control behavior.

Vascular neurocognitive disorder (multi-infarct neurocognitive disorder)

- Found in 15–30% of patients with neurocognitive disorder
- Risk factors: male, advanced age, hypertension, or other cardiovascular disorders
- Affects small and medium-sized vessels
- Examination may reveal carotid bruits, fundoscopic abnormalities, and enlarged cardiac chambers.
- MRI may reveal hyperintensities and focal atrophy suggestive of old infarctions.
- Deterioration may be stepwise or gradual, depending on underlying pathology.
- Focal neurologic symptoms (pseudobulbar palsy, dysarthria, and dysphagia are most common)
- Abnormal reflexes and gait disturbance are often present.
- Treatment is directed toward the underlying condition and lessening cell damage.
- Control of risk factors such as hypertension, smoking, diabetes, hypercholesterolemia, and hyperlipidemia is useful.

Table I-8-1. Alzheimer's Versus Vascular Neurocognitive Disorder

Alzheimer's	Vascular
Women	Men
Older age of onset	Younger than Alzheimer's patients
Chromosome 21	Hypertension
Linear or progressive deterioration	Stepwise or patchy deterioration
No focal deficits	Focal deficits
Supportive treatment	Treat underlying condition

Frontotemporal neurocognitive disorder (Pick disease)

- Neuroanatomic findings: atrophy in the frontal and temporal lobes
- Histopathology: Pick bodies (intraneuronal argentophilic inclusions) and Pick cells (swollen neurons) in affected areas of the brain
- Etiology is unknown.
- Most common in men with family history of Pick disease
- Difficult to distinguish from Alzheimer's
- May see features of Klüver-Bucy syndrome (hypersexuality, hyperphagia, passivity)

Neurocognitive disorder due to prion disease

- Rare spongiform encephalopathy is caused by a slow virus (prion).
- Presents with neurocognitive disorder, myoclonus, and EEG abnormalities (e.g., sharp, triphasic, synchronous discharges and, later, periodic discharges)
- Symptoms progress over months from vague malaise and personality changes to neurocognitive disorder and death.
- Findings include visual and gait disturbances, choreoathetosis or other abnormal movements, and myoclonus.
- Other prions that cause neurocognitive disorder (e.g., Kuru) may exist.

Neurocognitive disorder due to Huntington disease

- A rare, progressive neurodegenerative disease that involves loss of GABA-ergic neurons of the basal ganglia, manifested by choreoathetosis, neurocognitive disorder, and psychosis.
- Caused by a defect in an autosomal dominant gene located on chromosome 4
- Atrophy of the caudate nucleus, with resultant ventricular enlargement, is common.
- Clinical onset usually occurs at approximately age 40.
- Suicidal behavior is fairly common.

Neurocognitive disorder due to Parkinson disease

- Common, progressive, neurodegenerative disease involving loss of dopaminergic neurons in the substantia nigra
- Clinical onset is usually age 50–65.
- Motor symptoms include resting tremor, rigidity, bradykinesia, and gait disturbances.
- Neurocognitive disorder occurs in 40% of cases, and depressive symptoms are common.
- Destruction of dopaminergic neurons in the substantia nigra is a key pathogenic component and may be caused by multiple factors, including environmental toxins, infection, genetic predisposition, and aging.
- Treatment includes dopamine precursors (e.g., levodopa, carbidopa), dopamine agonists (e.g., bromocriptine), anticholinergic medications (e.g., benztropine, trihexyphenidyl), amantadine, and selegiline.
- Antiparkinsonian medications can produce personality changes, cognitive changes, and psychotic symptoms.

Neurocognitive disorder with Lewy bodies

- Hallucinations, parkinsonian features, and extrapyramidal signs
- Antipsychotic medications may worsen behavior
- Patients typically have fluctuating cognition, as well as REM sleep behavior disorder

Neurocognitive disorder due to HIV infection

- HIV directly and progressively destroys brain parenchyma; becomes clinically apparent in at least 30% of those with AIDS, beginning with subtle personality changes
- Diffuse and rapid multifocal destruction of brain structures occurs, and delirium is often present
- Motor findings: gait disturbance, hypertonia and hyperreflexia, pathologic reflexes (e.g., frontal release signs), and oculomotor deficits
- Mood disturbances: apathy, emotional liability, or behavioral disinhibition

Wilson disease

- Ceruloplasmin deficiency
- Hepatolenticular degeneration
- Kayser-Fleischer rings in the eye
- Asterixis

Normal pressure hydrocephalus

- Enlarged ventricles, normal pressure
- Neurocognitive disorder, urinary incontinence, and gait apraxia
- Treatment includes shunt placement

Note

(LBD) 1 yr ← PD → 1 yr (PDD)

Pseudodementia

- Typically seen in elderly patient who has a depressive disorder but appears to have symptoms of neurocognitive disorder; should improve after being treated with antidepressants
- Can usually date the onset of their symptoms

Table I-8-2. Pseudodementia versus Neurocognitive Disorder

Pseudodementia	Neurocognitive Disorder
Acute onset	Insidious onset
Family aware	Family unaware at first
Answers "I don't know" when asked questions	Confabulates when asked questions
Will talk about deficits when asked	Will minimize deficits
Treat with antidepressants	Will not improve with antidepressants

Table I-8-3. Delirium Versus Neurocognitive Disorder

Delirium	Neurocognitive Disorder
Acute onset	Insidious onset
Fluctuating course	Chronic course
Lasts days to weeks	Lasts months to years
Recent memory problems	Recent then remote memory problems
Disrupted sleep-wake cycle	Less disorientation at first
Disorientation	Normal sleep-wake cycle
Hallucinations common	Hallucinations, sundowning
Treat underlying condition	Supportive treatment

MILD NEUROCOGNITIVE DISORDER DUE TO SUBSTANCE/MEDICATION OR ANOTHER MEDICAL CONDITION

Definition. Characterized by prominent memory impairment in the absence of disturbances in level of alertness, or the other cognitive problems that are present with delirium or neurocognitive disorder

Risk Factors/Etiology (General Medical Conditions). Commonly associated with bilateral damage to diencephalic and mediotemporal structures (e.g., mammillary bodies, fornix, hippocampus). It may also be caused by conditions such as thiamine deficiency associated with alcohol dependence, head trauma, cerebrovascular disease, hypoxia, local infection (e.g., herpes encephalitis), ablative surgical procedures, and seizures.

Risk Factors/Etiology (Substances). Alcohol is likely the most common cause.

Table I-8-4. Wernicke Versus Korsakoff Syndromes

	Wernicke	Korsakoff
Course	Acute	Chronic
Reversibility	Yes	No
Presentation	Ataxia, nystagmus, and ophthalmoplegia	Confusion, psychosis, anterograde and retrograde amnesia
Treatment	Thiamine	Thiamine

Physical Examination. Evidence of chronic alcohol abuse is often present.

Treatment. Correction of the underlying pathophysiology (e.g., administration of thiamine in alcohol-induced amnestic disorder) may be effective in reversing or slowing the progression of symptoms.

Differential Diagnosis. Delirium, neurocognitive disorder, and dissociative amnesia are the common rule-outs.

Practice Question

A 65-year-old woman is found by the police in a filthy apartment after they were called by neighbors complaining of an unpleasant odor. Police find spoiled food in the kitchen, clogged sinks and toilets, and a severe infestation of cockroaches. The woman angrily refuses to leave with the police, stating that her neighbors have threatened her with attack and she fears that they will rob her apartment in her absence. Emergency room assessment reveals a very frail and unkempt woman who is completely alert and attentive. She believes it is 10 years earlier than it actually is, and she seems confused about her current finances and social contacts. She is unable to give the current addresses or phone numbers of her children and cannot find her phone book or purse. Physical exam is WNL. Which of the following disturbances is the most likely diagnosis?

(A) Vascular neurocognitive disorder
(B) Wernicke's syndrome
(C) Pseudodementia
(D) Delirium
(E) Neurocognitive disorder due to Alzheimer's disease

Answer: E. The woman presents with evidence of memory disturbance and severe problems managing her activities. This presentation is most consistent with neurocognitive disorder, which is characterized by memory impairment and other cognitive deficits. Vascular neurocognitive disorder often shows motor deficits on physical exam. Wernicke's shows more cognitive disturbance than just memory impairment. Pseudodementia occurs quickly and patients are aware of the symptoms. Delirium is characterized by problems with arousal and attention in addition to cognitive disturbance.

Dissociative Disorders 9

Learning Objectives

- ❑ Define depersonalization and derealization
- ❑ Describe the presentation of dissociative amnesia with and without fugue
- ❑ Recognize dissociative identity disorder

DISSOCIATION

Dissociation is a disconnection (lack of connection) between certain aspects of a person's consciousness that are usually associated with each other, such as memory, identity, and perception. Some degree of dissociation is normal; however, if an individual's consciousness becomes too fragmented, it may pathologically interfere with the sense of self and ability to adapt. Presenting complaints and findings of dissociative disorders include amnesia, personality change, erratic behavior, odd inner experiences (e.g., flashbacks, déjà vu), and confusion.

Dissociative Amnesia

Definition. Significant episodes in which the individual is unable to recall important and often emotionally charged memories. Dissociative amnesia **with fugue** also involves purposeful travel or bewildered wandering.

Risk Factors/Etiology. Psychological stress. More common in women and younger adults. Onset is usually detected retrospectively by the discovery of memory gaps of extremely variable duration.

Symptoms. Amnesia that may be general or selective for certain events. The amnesia may suddenly or gradually remit, particularly when the traumatic circumstance resolves, or may become chronic.

Associated Problems. Mood disorders, conversion disorder, and personality disorders are commonly present.

Treatment. Diagnostic evaluation for general medical conditions (e.g., head trauma, seizures, cerebrovascular disease) or substances (e.g., anxiolytic and hypnotic medications, alcohol) that may cause amnesia. Hypnosis, suggestion, and relaxation techniques are helpful. The patient should be removed from stressful situations when possible. Psychotherapy should be directed at resolving underlying emotional stress.

Differential Diagnosis. Major rule-outs are amnestic disorder due to a general medical condition, substance-induced amnestic disorder, and other dissociative disorders.

Dissociative Identity Disorder

Definition. Formerly called multiple personality disorder. Presence of multiple, distinct personalities that recurrently control the individual's behavior, accompanied by failure to recall important personal information.

Risk Factors/Etiology. Childhood sexual abuse has been postulated as a risk factor.

Prevalence. More common in women

Onset. Usually occult; clinical presentation is several years later when disturbances in interpersonal functioning are present.

Key Symptoms. Presence of distinct personalities is often subtle; in some cases, it is discovered only during treatment for associated symptoms.

Associated Problems. Chaotic interpersonal relationships, impulsivity and self-destructive behavior, suicide attempts, substance abuse

Comorbidity. Borderline personality disorder, PTSD, major depressive disorder and other mood disorders, substance-related disorders, sexual disorders, and eating disorders

Course. Symptoms may fluctuate or be continuous.

Differential Diagnoses. Borderline personality disorder and other personality disorders, bipolar disorder with rapid cycling, factitious disorder, and malingering

Treatment. Psychotherapy to uncover psychologically traumatic memories and to resolve the associated emotional conflict

Depersonalization and Derealization Disorder

Definition. Persistent or recurrent feeling of being detached from one's mental processes or body, accompanied by intact sense of reality

Risk Factors/Etiology. Psychologic stress

Prevalence. Episodes of depersonalization are common.

Onset. Usually in adolescence or early adulthood. Stressful events may precede the onset of the disorder.

Key Symptoms

- **Depersonalization:** often described as an "out-of-body experience"
- **Derealization:** Perception of the environment is often distorted or strange during episodes of depersonalization, accompanied by a feeling of being detached from physical surroundings. *Jamais vu* (a sense of familiar things being strange), déjà vu (a sense of unfamiliar things being familiar), and other forms of perceptual distortion may occur.

Associated Symptoms. Are often during episodes

Treatment. Psychotherapy directed at decreasing anxiety

Differential Diagnosis. Major rule-outs are substance-induced mental disorders with dissociative symptoms, including intoxication, withdrawal, hallucinogen-induced persisting perceptual disorder, panic disorder, and PTSD.

Practice Question

A 19-year-old man is brought to the emergency room by volunteers from a homeless shelter. The man claims that he cannot remember who he is. He says that he found himself in Los Angeles but that he cannot remember where he comes from, the circumstances of his trip, or any other information about his life. He has neither identification nor money, but he has a bus ticket from New York. Physical exam and laboratory testing are unremarkable. Which of the following is the most likely diagnosis?

(A) Depersonalization disorder
(B) Dissociative amnesia
(C) Dissociative amnesia fugue
(D) Dissociative identity disorder
(E) Substance-induced amnestic disorder

Answer: C. The symptoms of amnesia, unexplained travel, and identity confusion are most suggestive of dissociative fugue. Because of the generalized nature of his amnesia and negative physical findings, substance-induced amnestic disorder an unlikely diagnosis. There is insufficient evidence of distinct alternative personalities to diagnose dissociative identity disorder.

Adjustment Disorders 10

Learning Objectives

- ❑ Recognize and describe treatment approaches to adjustment disorders

ADJUSTMENT DISORDERS

Adjustment disorders are maladaptive reactions to an identifiable psychosocial stressor. They are caused by environmental stressors having an effect on functioning. The risk that a stressor will cause an adjustment disorder depends on one's emotional strength and coping skills.

Prevalence. Extremely common; all age groups. Onset is typically within 3 months of the initial presence of the stressor, and it lasts ≤6 months once the stressor is resolved. If the stressor continues and new ways of coping are not developed, it can become chronic.

Key Symptoms. Complaints of overwhelming anxiety, depression, or emotional turmoil associated with specific stressors

Associated Problems. Social and occupational performance deteriorate; erratic or withdrawn behavior

Treatment

- Remove or ameliorate the stressor
- Brief psychotherapy to improve coping skills
- Pharmacotherapy: Anxiolytic or antidepressant medications are used to ameliorate symptoms if therapy is not effective.

Differential Diagnosis. Normal reaction to stress. Disorders that occur following stress (e.g., GAD, PTSD, major depressive disorder).

Types

- Depressed mood
- Anxiety
- Mixed anxiety and depressed mood
- Disturbance of conduct
- Mixed disturbance of emotions and conduct

Practice Question

A 28-year-old woman without previous behavioral problems becomes angry and bitter after her husband of 5 years leaves her to live with his female business partner. One week later, the woman quits her job without giving notice and begins drinking heavily. For the next several weeks, the woman telephones friends and tearfully expresses her feelings. She also makes several threatening calls to her husband's new girlfriend. Which of the following is the most likely diagnosis?

(A) Adjustment disorder
(B) Alcohol-induced mood disorder
(C) Bipolar I disorder
(D) Bipolar II disorder
(E) Borderline personality disorder

Answer: A. Depression and erratic behavior after an interpersonal stressor are most suggestive of adjustment disorder with mixed disturbance of emotions and conduct. The cause of the symptoms is most likely the stressor and not the physiologic result of alcohol. Bipolar disorders I and II are unlikely diagnoses for an individual who has no history of mood episodes. Borderline personality disorder is a less likely diagnosis for an individual who has no history of past behavioral and interpersonal difficulties.

Substance-Related and Addictive Disorders

11

Learning Objectives

- ❑ Describe the neuroanatomy of substance-related and addictive disorders
- ❑ Present the epidemiology of addictive disorders
- ❑ Describe the behavioral and pharmacologic approaches to treating addicts

SUBSTANCE ABUSE AND ADDICTION

Definitions

- **Substance use disorder:** negative behavioral, cognitive, and/or physiologic symptoms due to use of a substance, yet use continues despite these adverse consequences
- **Intoxication:** reversible substance-specific syndrome due to recent use of a substance
- **Withdrawal:** substance-specific behavioral, cognitive, and/or physiologic change due to the cessation or reduction in heavy or prolonged substance use

Physical and Psychiatric Examination

- **Substance abuse history:** includes the substance(s) used, dosage(s), effects, duration and social context of use, and prior experiences with substance detoxification, rehabilitation, and relapse prevention
- **Medical history:** includes complications of substance abuse
- **Psychiatric history:** includes other primary psychiatric diagnoses and past treatments
- **Mental status examination:** includes signs of substance-induced disorders
- **Physical examination:** includes signs of substance use

Risk Factors/Etiology

- **Family history:** Biological sons of alcoholics are more likely to develop alcoholism than the general population.
- **Physiology:** Individuals who are innately more tolerant to alcohol may be more likely to develop alcohol abuse.
- **Developmental history:** poor parenting, childhood physical or sexual abuse, and permissive attitudes toward drug use
- **Environmental risk factors:** exposure to drug use through peers or certain occupations, economic disadvantage, and social isolation
- **Psychiatric disturbances:** conduct disorder, ADHD, depression, and low self-esteem

- **Self-medication hypotheses:** Individuals with certain psychologic problems may abuse substances in an effort to alleviate symptoms (e.g., a person suffering from an anxiety disorder uses alcohol to decrease innate anxiety).

Diagnostic Tests

CAGE. Affirmative answers to any 2 of the following questions (or to the last question alone) are suggestive of alcohol abuse:

- Have you ever felt that you should **C**ut down your drinking?
- Have you ever felt **A**nnoyed by others who have criticized your drinking?
- Have you ever felt **G**uilty about your drinking?
- Have you ever had a morning drink (**E**ye-opener) to steady your nerves or alleviate a hangover?

Urine drug screen: typically tests for amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, methadone, methaqualone, opiates, phencyclidine

Hair testing: typically tests for cocaine, amphetamines, methamphetamines, opiates, PCP, marijuana

Breath: typically tests for alcohol

Blood: increased AST, ALT, and GGT for alcohol abuse

Types of treatment

- **Pharmacotherapy:** medications that work on the reward center, such as naltrexone, varenicline, and bupropion
- **Psychotherapy:** preferably group therapy such as Alcoholics Anonymous, Narcotics Anonymous
- **Behavioral modification techniques:** disulfiram (aversive conditioning), patch, gum, inhaler (fading)
- **Detoxification units:** typically 5-10 days, provide medications to assure safe withdrawal from substances
- **Rehabilitation programs:** typically 28-day programs, learn about relapse prevention and identification of triggers

Table I-11-1. Blood Alcohol Level and Effect on Behavior

Blood Alcohol Level	Behavioral Effect
0.05%	Thought, judgment, and restraint are loosened and disrupted
0.1%	Motor actions become clumsy
0.2%	• Motor area of the brain is depressed • Emotional behavior is affected
0.3%	Confused or stuporous
0.4–0.5%	• Coma • At higher levels, death may occur due to respiratory depression

Table I-11-2. Substances of Abuse

Substance	Signs and Symptoms of Intoxication	Treatment of Intoxication	Signs and Symptoms of Withdrawal	Treatment of Withdrawal
Alcohol	Talkativeness, sullenness, gregariousness, moodiness, etc.	Mechanical ventilation, if severe	Tremors, hallucinations, seizures, delirium tremens	Benzodiazepines Thiamine Multivitamin Folic acid
Amphetamines, cocaine	Euphoria, hypervigilance, autonomic hyperactivity, weight loss, papillary dilatation, perceptual disturbances	Short-term use of antipsychotics, benzodiazepines, vitamin C to promote excretion in urine, antihypertensives	Anxiety, tremulousness, headache, increased appetite, depression, risk of suicide	Antidepressants
Anabolic steroids	Irritability, aggression, mood changes, psychosis, heart problems, liver problems, etc.	Symptomatic, abstinence	Depression, risk of suicide	SSRIs
Bath salts	Headache, palpitations, hallucinations, paranoia, violence, increased heart rate and blood pressure	Supportive, benzodiazepines	Unknown	Unknown
Benzodiazepines	Inappropriate sexual or aggressive behavior, impairment in memory or concentration	Flumazenil	Autonomic hyperactivity, tremors, insomnia, seizures, anxiety	Benzodiazepines
Cannabis	Impaired motor coordination, slowed sense of time, social withdrawal, conjunctival injection, increased appetite, dry mouth, tachycardia	None	None	None
Ecstasy	Euphoria, mild psychedelia, hyponatremia, seizures, death, rhabdomyolysis, increased heart rate, blood pressure, and temperature	Cyproheptadine, benzodiazepines, dantrolene	Unknown	Unknown
Hallucinogens	Ideas of reference, perceptual disturbances, impaired judgment, dissociative symptoms, pupillary dilatation, tremors, incoordination	Supportive counseling (talking down), antipsychotics, benzodiazepines	None	None

(*Continued*)

Table I-11-2. Substances of Abuse (*Cont'd*)

Substance	Signs and Symptoms of Intoxication	Treatment of Intoxication	Signs and Symptoms of Withdrawal	Treatment of Withdrawal
Inhalants	Belligerence, apathy, assaultiveness, impaired judgment, blurred vision, stupor or coma	Antipsychotics if delirious or agitated	None	None
Opiates	Apathy, dysphoria, papillary constriction, drowsiness, slurred speech, impairment in memory, coma or death	Naloxone	Fever, chills, lacrimation, runny nose, abdominal cramps, muscle spasms, insomnia, yawning	Clonidine, methadone
Phencyclidine (PCP)	Belligerence, assaultiveness, psychomotor agitation, nystagmus, hypertension, seizures, coma, hyperacusis	Talking down, benzodiazepines, antipsychotics	None	None

Practice Question

A 29-year-old man is brought in by judicial order for evaluation of his continued involvement with heroin use. The man denies that he is addicted but is willing to enter treatment to avoid more severe criminal penalties. Which of the following is essential to determine the presence of heroin use disorder in this individual?

(A) A family history of substance abuse
(B) Numerous arrests for dealing heroin
(C) He vehemently denies that his use of heroin causes him any problems
(D) He spends all his time trying to obtain heroin and can't stop himself from using it
(E) He is not cooperative with treatment planning

Answer: D. Substance use disorder is characterized by the presence of a constellation of symptoms that suggest compulsive substance use, monopolization of time by substance-related activities, social and occupational consequences, and physiologic changes including tolerance and withdrawal. A family history of substance abuse, arrests for drug dealing, denial of substance-related problems, and cooperation with treatment may all occur in individuals with substance dependence, but are not diagnostic when occurring by themselves.

Impulse Control Disorders 12

Learning Objectives

- ❏ Describe the presentation of intermittent explosive disorder, kleptomania, pyromania, gambling disorder, and trichotillomania
- ❏ Describe the treatment approaches for impulse control disorders

IMPULSE CONTROL

In impulse control disorders, patients are unable to resist a negative impulse. Before the act they have increased anxiety, and after the act they feel a reduction in anxiety. Impulse control is mediated by the serotonergic system.

INTERMITTENT EXPLOSIVE DISORDER

> The police arrest a 24-year-old man after he beats up an older man, causing severe injury to his head and neck area and requiring more than 100 stitches. When asked why he assaulted the older man, he replies, "He took my potato chips."

Definition. A disorder characterized by discrete episodes of failure to resist aggressive impulses that result in serious assaultive acts or destruction of property. The degree of the aggressive act is typically out of proportion to the stressor. The attacks may occur within minutes or hours and tend to resolve spontaneously.

Risk Factors/Epidemiology. Affects men more than women, especially men in prisons and women in psychiatric facilities. May have genetic linkage because it is seen frequently among first-degree relatives. Patients may have had a history of head trauma, seizures, encephalitis, hyperactivity, or other brain dysfunction. May be linked to low levels of 5HIAA, abnormalities in the limbic system, or testosterone. The symptoms lessen as the patients age.

Physical and Psychiatric Presenting Symptoms

- Neurologic examination may reveal soft signs, such as right–left ambivalence
- EEG usually normal
- Psychologic tests often normal
- Poor work histories
- Marital difficulties
- Problems with the law

Treatment. Pharmacotherapy consisting of anticonvulsants, antipsychotics, beta-blockers, or SSRIs has been somewhat helpful. Psychotherapy, although not the preferred treatment, may be beneficial. When psychotherapy is used, it must be with pharmacotherapy and in a group setting.

Differential Diagnosis

- **Medical:** epilepsy, brain tumors, degenerative disease, and endocrine disorders
- **Psychiatric:** antisocial personality disorder, borderline personality disorder, schizophrenia, and substance intoxication

KLEPTOMANIA

A 25-year-old woman has a history of more than 20 arrests for stealing small items. She comes from a wealthy family and her parents do not understand her behavior. At home she has numerous salt and pepper shakers, napkin rings, and ashtrays, none of which she needs.

Definition. A disorder characterized by the recurrent failure to resist impulses to steal objects that the patient does not need. There is increased anxiety prior to the act, followed by release of anxiety after the act. The act of stealing is the goal.

Risk Factors/Epidemiology. Appears to be more common in women. Symptoms may be linked to stress in the patient's life. Often associated with mood disorders, OCDs, and eating disorders such as bulimia nervosa. It has been linked to brain disease and ID.

Physical and Psychiatric Presenting Symptoms. May have signs of anxiety and depression. Feel guilty or ashamed of their actions.

Treatment. Insight-oriented therapy may be indicated to help the patients understand their behavior. Behavioral therapy, including aversive conditioning and systematic desensitization, has been helpful in some patients. If pharmacotherapy is indicated, consider SSRIs or anticonvulsants.

Differential Diagnosis

- **Medical:** none
- **Psychiatric:** antisocial personality disorder, malingering, mania, and schizophrenia

PYROMANIA

A 19-year-old teen with mild ID is arrested after he is found setting the neighbor's garbage cans on fire. Neighbors had observed him in the past starting fires in his own backyard, staring at them for hours, watching them burn.

Definition. A disorder characterized by deliberate fire-setting on more than one occasion. There is anxiety before the act and a release of anxiety after the act, sometimes followed by fascination and gratification. Must rule out arson.

Risk Factors/Epidemiology. Seen more frequently in men who are mildly retarded and may have a history of alcohol abuse. Many have histories of truancy and cruelty to animals.

Physical and Psychiatric Presenting Symptoms. Many watch fires in their neighborhoods and/or set off fire alarms. Lack remorse for the consequences of their actions and show resentment toward authority figures. May become sexually aroused by the fire.

Treatment. Because no treatment has been proven to be beneficial, incarceration may be indicated.

Differential Diagnosis

- **Medical:** brain dysfunctions
- **Psychiatric:** antisocial personality disorder, conduct disorder, mania, and schizophrenia

GAMBLING DISORDER

> A 40-year-old married man and father was fired from his job because of embezzlement of company funds, which he used to gamble with. When found, he did not have the money on him and admitted to losing it at a casino. His wife left him 2 months ago, and he has not seen his wife or children since then.

In DSM-5, this is now included under Substance-Related and Addictive Disorders.

Definition. A disorder characterized by persistent and recurrent gambling behavior that includes a preoccupation with gambling, a need to gamble with more money, attempts to stop gambling and/or to win back losses, illegal acts to finance the gambling, or loss of relationships due to gambling.

Risk Factors/Epidemiology. More common in men, and seen in their parents as well. Increased incidence of alcohol dependence. May be predisposed by death, loss of a loved one, poor parenting, exposure to gambling behavior, and/or divorce. May be linked to mood disorders, OCDs, panic disorder, agoraphobia, and ADHD.

Physical and Psychiatric Presenting Symptoms

- May engage in antisocial behavior to obtain money for gambling
- Appear overconfident
- Suicide attempts
- Multiple arrests and/or incarceration

Treatment. Gamblers anonymous (GA) is the most effective treatment. It involves public confessions, peer pressure, and sponsors. Although pharmacotherapy is usually not indicated, some studies have shown some efficacy with SSRIs.

Differential Diagnosis

- **Medical:** none
- **Psychiatric:** mania, antisocial personality disorder

TRICHOTILLOMANIA

A 20-year-old woman is rushed to the hospital after she complains of severe abdominal pain. She appears thin and withdrawn and is missing a lot of hair from both her scalp and eyebrows. A physical examination reveals an intestinal obstruction.

In DSM-5, this is now included under Obsessive-Compulsive and Related Disorders.

Definition. A disorder characterized by pulling one's own hair, resulting in hair loss. There is anxiety before the act and a release of anxiety after the act.

Risk Factors/Epidemiology. Affects women more than men. Associated disorders include OCD, obsessive-compulsive personality disorder, and depressive disorders.

Physical and Psychiatric Presenting Symptoms

- Hair loss is significant over all areas of the body.
- Area most affected is the scalp.
- May eat the hair, resulting in bezoars, obstruction, and malnutrition
- Head-banging, nail-biting, and gnawing may be present.
- Examination of the scalp reveals short, broken hairs along with long hairs.

Treatment. Treatment usually consists of behavior-modification techniques to decrease patient's anxiety as well as pharmacotherapy such as SSRIs, anticonvulsants, or antipsychotics to help decrease the urges.

Differential Diagnosis

- **Medical:** alopecia areata, tinea capitis (biopsy would be indicated)
- **Psychiatric:** OCD, factitious disorder

Practice Question

A 22-year-old woman was recently seen at her college graduation hoarding food in her purse and briefcase. When asked why, she replied, "I might be hungry later." She appeared to be of average height and weight, but with poor dentition. She has numerous calluses on the backs of both hands. Which of the following disorders is she at risk for developing?

(A) Trichotillomania
(B) Kleptomania
(C) Gambling disorder
(D) Pyromania
(E) Intermittent explosive disorder

Answer: B. Patients with bulimia nervosa have an increased incidence of kleptomania. These patients will steal things they do not need.

Eating Disorders 13

Learning Objectives

- ❑ List the diagnostic criteria for anorexia nervosa, bulimia nervosa, and binge eating disorder
- ❑ Describe treatment approaches for the various eating disorders
- ❑ List criteria for admission of a patient with an eating disorder

ANOREXIA NERVOSA

Definition. Characterized by failure to maintain a normal body weight, fear and preoccupation with gaining weight, and unrealistic self-evaluation as overweight. Subtypes are restricting (no binge-eating or purging) and binge-eating/purging (regularly engaged in binge-eating/purging).

Risk Factors/Etiology. Biologic factors are suggested by higher concordance for illness in monozygotic twins and the fact that amenorrhea may precede abnormal eating behavior. Psychologic risk factors include emotional conflicts concerning family control and sexuality. A cultural risk factor may be an emphasis on thinness.

Prevalence. 0.5%. Occurs at a 1:10 male-to-female ratio.

Onset. Average age is 17 years. Very late–onset anorexia nervosa has a poorer prognosis. Onset is often associated with emotional stressors, particularly conflicts with parents about independence, and sexual conflicts.

Key Symptoms

- Restricted food intake and maintaining diets of low-calorie foods. Weight loss may also be achieved through purging (i.e., vomiting or taking laxatives, diuretics, or enemas) and exercise.
- Great concern with appearance. Significant amount of time spent examining and denigrating self for perceived signs of excess weight.
- Denial of emaciated conditions
- With binge-eating/purging: self-induced vomiting; laxative and diuretic abuse

Associated Symptoms. Excessive interest in food-related activities (other than eating), obsessive-compulsive symptoms, depressive symptoms

Course. Some individuals recover after a single episode, and others develop a waxing-and-waning course.

Outcome. Long-term mortality rate of individuals hospitalized for anorexia nervosa is 10%, resulting from the effects of starvation and purging or suicide.

Physical Examination. Signs of malnutrition include emaciation, hypotension, bradycardia, lanugo (i.e., fine hair on the trunk), and peripheral edema. Signs of purging include eroded dental enamel caused by emesis and scarred or scratched hands from self-gagging to induce emesis. There may be evidence of general medical conditions caused by abnormal diets, starvation, and purging.

Diagnostic Tests

- **Signs of malnutrition:** normochromic, normocytic anemia, elevated liver enzymes, abnormal electrolytes, low estrogen and testosterone levels, sinus bradycardia, reduced brain mass, and abnormal EEG
- **Signs of purging:** metabolic alkalosis, hypochloremia, and hypokalemia caused by emesis; metabolic acidosis caused by laxative abuse

Treatment. Initial treatment should be correction of significant physiologic consequences of starvation with hospitalization if necessary. Behavioral therapy should be initiated, with rewards or punishments based on absolute weight, not on eating behaviors. Family therapy designed to reduce conflicts about control by parents is often helpful. Antidepressants may play a limited role in treatment when comorbid depression is present.

Differential Diagnosis. Major rule-outs are bulimia nervosa, general medical conditions that cause weight loss, major depressive disorder, schizophrenia, OCD, and body dysmorphic disorder.

BULIMIA NERVOSA AND BINGE EATING DISORDER

Definition. Characterized by frequent binge-eating and a self-image that is unduly influenced by weight. Types:

- **Bulimia nervosa:** binge-eating and purging behavior
- **Binge-eating disorder:** binge-eating but no purging behavior

Risk Factors/Etiology. Psychologic conflict regarding guilt, helplessness, self-control, and body image may predispose. Biologic factors are suggested by frequent association with mood disorders.

Prevalence. 2% in young adult females. Occurs at a 1:9 male-to-female ratio.

Onset. Usually during late adolescence or early adulthood and often follows a period of dieting

Course. May be chronic or intermittent

Outcome. 70% of cases have remitted after 10 years. Co-occurring substance abuse is associated with a poorer prognosis.

Key Symptoms

- **Recurrent episodes of binge-eating in both binge-eating disorder and bulimia.** Obsession with dieting but followed by binge-eating of high-calorie foods. Binges are associated with emotional stress and followed by feelings of guilt, self-recrimination, and compensatory behaviors.
- **Recurrent, inappropriate compensatory behavior in bulimia but not in binge-eating disorder.** After a binge, attempts to prevent weight gain through self-induced vomiting, misuse of laxatives, diuretics, enemas, or other medications; fasting; or excessive exercise.
- **Self-evaluation is unduly influenced by body shape and weight in bulimia.** Self-castigation for mild weight gain or binges. Attempts to conceal binge-eating or purging, or lies about behaviors.

Associated Problems. Depressive symptoms, substance abuse, and impulsivity (e.g., kleptomania)

Comorbid Disorders. Borderline personality disorder present in about 50%

Physical Examination. Evidence of purging

Diagnostic Tests. Evidence of laxative or diuretic abuse

Treatment. Cognitive and behavioral therapy are major treatment. Psychodynamic psychotherapies are useful for accompanying borderline personality traits. Antidepressant medications, particularly SSRIs, are usually employed.

Differential Diagnosis. Major rule-outs are anorexia nervosa, binge-eating/purging, major depressive disorder with atypical features, and borderline personality disorder.

Practice Question

A 19-year-old woman is hospitalized for dehydration caused by severe, laxative-induced diarrhea. She is depressed about the recent breakup of a romantic relationship. She admits that she uses laxatives because she has been binge-eating frequently and is worried about gaining weight. Although the woman has BMI 16, she believes that she is overweight. Which of the following is the most likely diagnosis?

(A) Anorexia nervosa
(B) Brief psychotic disorder
(C) Bulimia nervosa
(D) Delusional disorder, somatic type
(E) Major depressive disorder

Answer: A. The patient presents with low body weight, a distorted body image, a fear of obesity, and amenorrhea, all which strongly suggest anorexia nervosa. Bingeing and purging behavior is commonly present with this disorder. Because this individual has the essential features of anorexia nervosa, the diagnosis of bulimia nervosa is not made. Because the woman shows no evidence of delusions, brief psychotic disorder or delusional disorder are unlikely diagnoses. Although depression commonly accompanies eating disorders, it does not appear to be the primary problem in this woman's case.

Personality Disorders 14

Learning Objectives

- ❑ List the most common personality criteria and their diagnostic criteria

PERSONALITY DISORDERS

Personality disorders (PDs) are characterized by personality patterns that are pervasive, inflexible, and maladaptive. There are 3 clusters:

Cluster A: peculiar thought processes, inappropriate affect

Cluster B: mood lability, dissociative symptoms, preoccupation with rejection

Cluster C: anxiety, preoccupation with criticism or rigidity

Risk Factors/Etiology. PDs are the product of the interaction of inborn temperament and subsequent developmental environment. Risk factors include innate temperamental difficulties, such as irritability; adverse environmental events, such as child neglect or abuse; and personality disorders in parents.

Prevalence. All are relatively common. More males have antisocial and narcissistic PDs, more females have borderline and histrionic PDs.

Onset. Usually not diagnosed until late adolescence or early adulthood

Course. Usually very chronic over decades without treatment. Symptoms of paranoid, schizoid, and narcissistic PD often worsen with age; symptoms of antisocial and borderline PD often ameliorate.

Key Symptoms. Long pattern of difficult interpersonal relationships, problems adapting to stress, failure to achieve goals, chronic unhappiness, low self-esteem

Associated Diagnoses. Mood disorders

Treatment. Psychotherapy is the mainstay of treatment. Intensive and long-term psychodynamic and cognitive therapy are treatments of choice for most PDs. Use of mood stabilizers and antidepressants is sometimes useful for Cluster B PDs.

Differential Diagnosis. Major rule-outs are mood disorders, personality change due to a general medical condition, and adjustment disorders.

Cluster A

Paranoid PD: Distrust and suspiciousness. Individuals are mistrustful and suspicious of the motivations and actions of others and are often secretive and isolated. They are emotionally cold and odd.

> A 57-year-old man living in a condominium complex constantly accuses his neighbors of plotting to avoid payment of their share of maintenance. He writes angry letters to other owners and has initiated several lawsuits. He lives alone and does not socialize.

Schizoid PD: Detachment and restricted emotionality. Individuals are emotionally distant. They are disinterested in others and indifferent to praise or criticism. Associated features include social drifting and dysphoria.

> A 24-year-old man lives alone and works nights as a security guard. He ignores invitations from coworkers to socialize and has no outside interests.

Schizotypal PD: Discomfort with social relationships; thought distortion; eccentricity. Individuals are socially isolated and uncomfortable with others. Unlike Schizoid PD, they have peculiar patterns of thinking, including ideas of reference and persecution, odd preoccupations, and odd speech and affect. DSM-5 includes this PD in both psychotic disorders and personality disorders.

> A 30-year-old man is completely preoccupied with the study and the brewing of herbal teas. He associates many peculiar powers with such infusions and says that plants bring him extra luck. He spends all of his time alone, often taking solitary walks in the wilderness for days at a time, collecting plants for teas. He has no history of disorganized behavior. At times he believes that songs on the radio are about his life.

Cluster B

Histrionic PD. Usually characterized by colorful, exaggerated behavior and excitable, shallow expression of emotions; uses physical appearance to draw attention to self; sexually seductive; and is uncomfortable in situations where he or she is not the center of attention.

> A 30-year-old woman presents to the doctor's office dressed in a sexually seductive manner and insists that the doctor comment on her appearance. When the doctor refuses to do so, she becomes upset.

Borderline PD. Usually characterized by an unstable affect, mood swings, marked impulsivity, unstable relationships, recurrent suicidal behaviors, chronic feelings of emptiness or boredom, identity disturbance, and inappropriate anger. If stressed, may become psychotic. Main defense mechanism is splitting.

> A 20-year-old nurse was recently admitted after reporting auditory hallucinations, which have occurred during the last few days. She reports marriage difficulties and believes her husband is to blame for the problem. She has several scars on her wrists and has a history of substance abuse.

Antisocial PD. Usually characterized by continuous antisocial or criminal acts, inability to conform to social rules, impulsivity, disregard for the rights of others, aggressiveness, lack of remorse, and deceitfulness. These have occurred since the age of 15, and the individual is at least 18 years of age.

> A 22-year-old man was recently arrested after he set his mother's house on fire. He has had numerous problems with the law, which started at an early age when he was sent to a juvenile detention center for his behavior at both home and school. He lacks remorse for setting the fire and expresses a desire that his mother would have died in the fire.

Narcissistic PD. Usually characterized by a sense of self-importance, grandiosity, and preoccupation with fantasies of success. This person believes he is special, requires excessive admiration, reacts with rage when criticized, lacks empathy, is envious of others, and is interpersonally exploitative.

> A famous actor is outraged when a director questions his acting abilities during rehearsal for a play. The actor responds by walking off the stage and not returning to the stage unless the director apologizes publicly for her behavior.

Cluster C

Avoidant PD. Individuals have social inhibition, feelings of inadequacy, and hypersensitivity to criticism. They shy away from work or social relationships because of fears of rejection that are based on feelings of inadequacy. They feel lonely and substandard and are preoccupied with rejection.

> A 43-year-old man dreads an upcoming company holiday party because he believes that he is incapable of engaging in social conversation or dancing. He believes that he will become an object of pity or ridicule if he attempts such things. He anticipates yet another lonely holiday.

Dependent PD: Submissive and clinging behavior related to a need to be taken care of. Individuals are consumed with the need to be taken care of. They have clinging behavior and worry unrealistically about abandonment. They feel inadequate and helpless and avoid disagreements with others. They usually focus dependency on a family member or spouse and desperately seek a substitute should this person become unavailable. Associated features include self-doubt, excessive humility, poor independent functioning, mood disorders, anxiety disorders, adjustment disorder, and other PDs.

> A 26-year-old man is brought into the emergency room after sustaining severe rectal lacerations during a sadistic sexual episode with his partner. The patient is extremely concerned that the police not be informed because he doesn't want to upset his partner and cause the partner to leave.

Obsessive-Compulsive PD. Individuals are preoccupied with orderliness, perfectionism, and control. They are often consumed by the details of everything and lose their sense of overall goals. They are strict and perfectionistic, overconscientious, and inflexible. They may be obsessed with work and productivity and are hesitant to delegate tasks to others. Other traits include being miserly and unable to give up possessions. This PD should not be confused with OCD, a separate disorder. Associated features include indecisiveness, dysphoria, anger, social inhibition, and difficult interpersonal relationships.

> A 37-year-old woman seeks psychotherapy as a result of an impending divorce. She states that her demands to keep the house spotless, to maintain an extremely detailed and fixed work and recreational schedule, and to observe rigid dietary habits have driven her spouse away.

Normal Sleep and Sleep Disorders

15

Learning Objectives

- ❑ Identify the normal sleep cycles
- ❑ Describe EEG, ENG, and physiologic phenomenon associated with each stage of sleep
- ❑ Categorize different sleep disorders and describe what is known about their causes

NORMAL SLEEP

Sleep is divided into 2 stages: nonrapid eye movement (NREM) and rapid eye movement (REM). There are numerous differences between them.

NREM

NREM is a state of sleep characterized by slowing of the EEG rhythms, high muscle tone, absence of eye movements, and thoughtlike mental activity. The brain is inactive while the body is active. NREM is made up of 4 stages.

Table I-15-1. NREM

Stage	EEG Findings	Distribution
Stage 1	Disappearance of alpha wave and appearance of theta wave	5%
Stage 2	K-complexes and sleep spindles	45%
Stage 3	Appearance of delta wave	12%
Stage 4	Continuation of delta wave	13%

REM

REM is a stage of sleep characterized by aroused EEG patterns, sexual arousal, saccadic eye movements, generalized muscular atony (except middle-ear and eye muscles), and dreams. The brain is active and the body is inactive.

Table I-15-2. REM

Stage	EEG Findings	Distribution
REM	Bursts of sawtooth waves	25%

Sleep Facts

Table I-15-3. Sleep Facts (Stage 2–REM)

Stage	Fact(s)
Stage 2	Longest of all the sleep stages
Stages 3 and 4	Also called slow wave or delta sleep Hardest to arouse Tends to vanish in the elderly
REM	Easiest to arouse Lengthens in time as night progresses Increased during the second half of the night

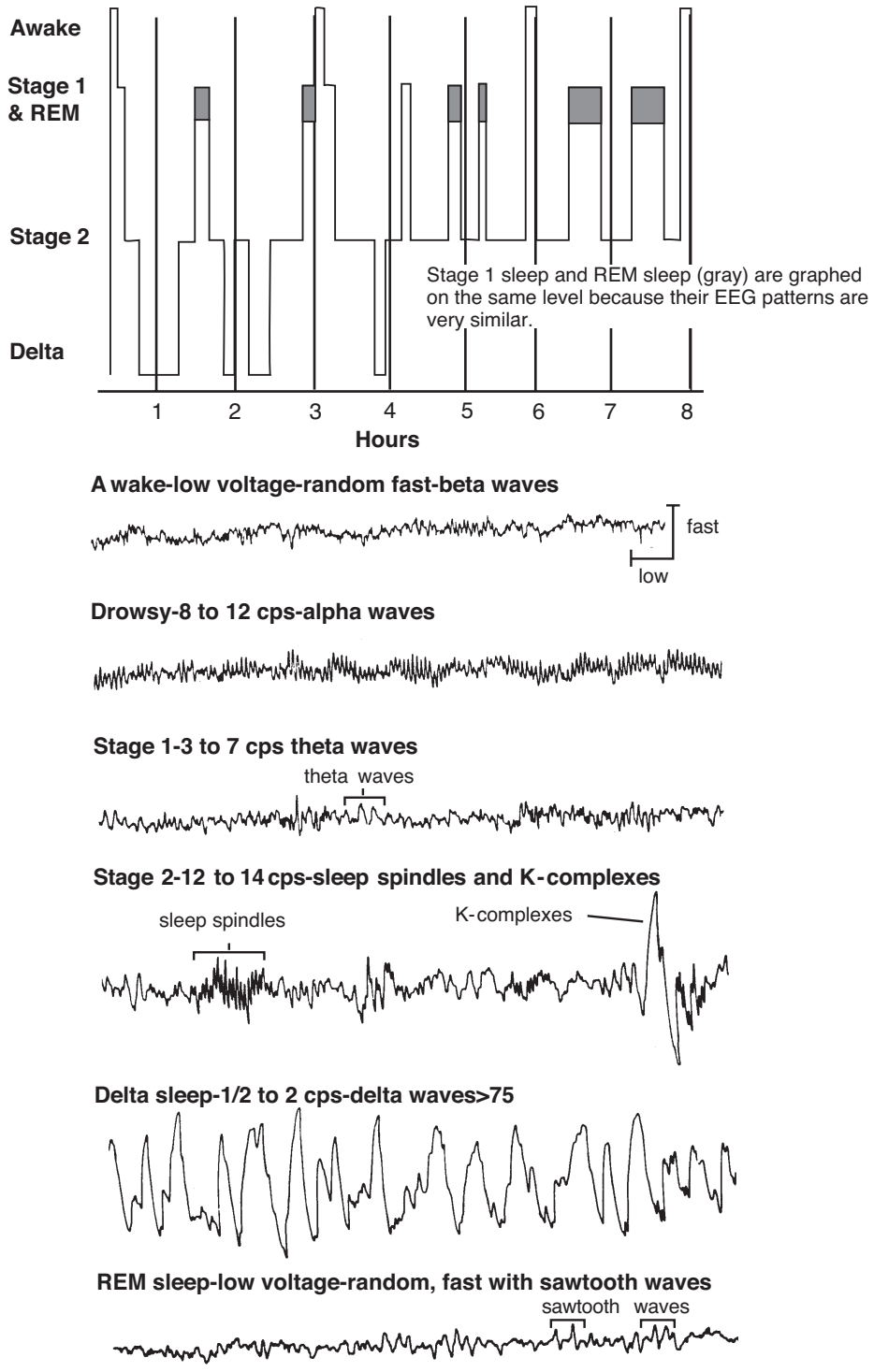


Figure I-15-1. Sleep Architecture Diagram Showing Stages of Sleep in Sequence

Sleep Latency. The time needed before you actually fall asleep. Typically less than 15 minutes in most individuals; however, may be abnormal in many disorders, such as insomnia, etc.

REM Latency. The period lasting from the moment you fall asleep to the first REM period. Lasts approximately 90 minutes in most individuals. However, several disorders will shorten REM latency; these disorders include depression and narcolepsy.

Characteristics of Sleep from Infancy to Old Age

- Total sleep time decreases.
- REM percentage decreases.
- Stages 3 and 4 tend to vanish.

Neurotransmitters of Sleep

- **Serotonin:** increased during sleep; initiates sleep
- **Acetylcholine:** increased during sleep; linked to REM sleep
- **Norepinephrine:** decreased during sleep; linked to REM sleep
- **Dopamine:** increased toward end of sleep; linked to arousal and wakefulness

Chemical Effects on Sleep

- **Tryptophan:** increases total sleep time
- **Dopamine agonists:** produce arousal
- **Dopamine antagonists:** decrease arousal, thus produce sleep
- **Benzodiazepines:** suppress Stage 4 and, when used chronically, increase sleep latency
- **Alcohol intoxication:** suppresses REM
- **Barbiturate intoxication:** suppresses REM
- **Alcohol withdrawal:** REM rebound
- **Barbiturate withdrawal:** REM rebound
- **Major depression:** shortened REM latency, increased REM time, suppression of delta, multiple awakenings, and early morning awakening

SLEEP DISORDERS

Narcolepsy

> A 35-year-old man was recently hospitalized for the tenth time after he crashed his car into a post. When questioned, he did not remember the cause of the accident and had just had his license suspended. His friends reported occasions when he fell asleep during dinner and during conversations with them.

Definition. A disorder characterized by excessive daytime sleepiness and abnormalities of REM sleep for a period of greater than 3 months. REM sleep occurs in less than 10 minutes. Patients feel refreshed upon awakening.

Physical and Psychiatric Presenting Symptoms

- **Sleep attacks:** most common symptom
- **Cataplexy:** Pathognomonic sign, consisting of a sudden loss of muscle tone that may have been precipitated by a loud noise or intense emotion. If short episode, the patient remains awake.
- **Hypnagogic and hypnopompic hallucinations:** Hallucinations that occur as the patient is going to sleep and is waking up from sleep, respectively.
- **Sleep paralysis:** Most often occurs during awakening, when the patient is awake but unable to move.
- Report falling asleep quickly at night

Treatment. Forced naps at a regular time of day are usually the treatment of choice. When medications are given, psychostimulants are preferred. If cataplexy is present, antidepressants such as TCAs are preferred. Gamma-hydroxybutyrate (GHB) is also used for narcolepsy–cataplexy by improving the quality of nighttime sleep.

Sleep Apnea

An overweight man reports having difficulties in his marriage because of his snoring at night. During the day, he reports feeling tired despite sleeping for 8 hours at night.

Definition. A disorder characterized by the cessation of airflow at the nose or mouth during sleep. These apneic episodes usually last longer than 10 seconds each. Characterized by a loud snore followed by a heavy pause. Considered pathologic if the patient has more than 5 episodes an hour or more than 30 episodes during the night. In severe cases, patients may experience more than 300 apneic episodes during the night.

Physical and Psychiatric Presenting Symptoms

- Usually seen in obese, middle-aged males
- Sometimes associated with depression, mood changes, and daytime sleepiness
- Spouses typically complain of partner's snoring, and of partner's restlessness during the night
- Complain of dry mouth in the morning
- May have headaches in the morning
- Complain of being tired during the day
- May develop arrhythmias, hypoxemia, pulmonary hypertension, and sudden death

Types of Sleep Apnea

- **Obstructive:** muscle atonia in oropharynx; nasal, tongue, or tonsil obstruction
- **Central:** lack of respiratory effort
- **Mixed:** central at first, but prolonged due to collapse of the airway

Treatment. Continuous positive nasal airway pressure is the treatment of choice. Other treatment includes weight loss, surgery. Sleeping on one's side instead of one's back will help keep the airways open.

Insomnia

> While studying over the past week for an important exam, Michael, a third-year medical student, has been unable to sleep for the past several days. At night, he lies awake and imagines himself doing poorly on the exam and failing medical school. During the day, he is tired and frequently falls asleep during his classes.

Definition. A disorder characterized by difficulties in initiating or maintaining sleep

Risk Factors/Epidemiology. Typically associated with some form of anxiety or anticipatory anxiety. Many patients have underlying psychiatric disorders, such as depression, etc. If due to a psychiatric disorder, seen more frequently in women. Other conditions include PTSD, OCD, and eating disorders.

Physical and Psychiatric Presenting Symptoms

- Predominant complaint is difficulty initiating or maintaining sleep
- Affects the patient's level of functioning
- Frequent yawning and tiredness during the day

Treatment. Consider good sleep hygiene techniques, such as arising at same time of the day, avoiding daytime naps, avoiding evening stimulation, discontinuing CNS-acting drugs, taking hot baths near bedtime, eating meals at regular times, using relaxation techniques, and maintaining comfortable sleeping conditions. If these do not work, consider behavioral modification techniques such as stimulus control. If medications are to be used, consider zolpidem, eszopiclone, or zaleplon.

Differential Diagnosis

- **Medical:** pain, CNS lesions, endocrine diseases, aging, brain-stem lesions, alcohol, diet, medications
- **Psychiatric:** anxiety, tension, depression, and environmental changes, other sleep disorders

Parasomnias

Table I-15-4. Parasomnias

Disorder	Sleep Stage	Characteristics	Treatment
Nightmares (dream anxiety disorder)	REM	• Memory of the event upon awakening • Increases during times of stress • Reported by 50% of the population	• Usually none indicated, but may use REM suppressants such as TCAs
Night terrors (sleep terror disorder)	Stages 3 and 4	• Awakened by scream or intense anxiety • No memory of the event the following day • Seen more frequently in children • More common in boys • Runs in families	• Treatment rarely required • If medication is needed, consider benzodiazepines
Sleeptalking	All stages of sleep	• Common in children • Usually involves a few words • May accompany night terrors and sleepwalking	• No treatment is necessary
Sleepwalking	Stage 3 and 4	• Sequence of behaviors without full consciousness • May perform perseverative behaviors • Usually terminates in awakening followed by confusion • May return to sleep without any memory of the event • Begins at a young age • More common in boys • May find neurologic condition • Sleep deprivation may exacerbate	• Need to assure patient safety • Use medication such as benzodiazepines to suppress stages 3 and 4

Practice Questions

1. An overweight man of average height presents to his doctor's office complaining of feeling tired during the day. He has missed several days of work due to this problem. Which of the following is the most likely diagnosis?

   (A) Narcolepsy
   (B) Insomnia
   (C) Sleep apnea
   (D) Normal sleep pattern
   (E) Hypersomnia

2. Which of the following is the most likely explanation for a young man suddenly falling down but not losing consciousness?

   (A) Syncope
   (B) Cataplexy
   (C) Sleep paralysis
   (D) Medication toxicity
   (E) Hypotensive episode

3. Which of the following is the treatment of choice for insomnia?

   (A) Long-term use of benzodiazepines
   (B) Behavioral techniques
   (C) Drinking coffee before bedtime
   (D) Regular exercises before bedtime
   (E) Frequent naps during the day

1. **Answer: C.** Patients with sleep apnea have multiple episodes of waking up in the middle of the night. Therefore, they are tired during the day. These patients are typically unaware that they wake in the middle of the night.
2. **Answer: B.** Cataplexy is the sudden loss of muscle tone without loss of consciousness. It is differentiated from syncope in that syncope typically includes loss of consciousness. Patients with narcolepsy are usually young and do not have any blood pressure abnormalities.
3. **Answer: B.** Although benzodiazepines are regularly used for the treatment of insomnia, the best treatment includes behavioral techniques such as stimulus control. The patient leaves the bed whenever he is unable to fall asleep, therefore conditioning himself that the bed is only used for sleeping. Choices C, D, and E will tend to cause insomnia.

Human Sexuality 16

Learning Objectives

- ❑ Present epidemiologic information about masturbation and homosexuality
- ❑ List the types of sexual dysfunction and differentiating factors
- ❑ Describe paraphilic disorder and gender dysphoria

SEXUALITY

Sexual identity is based on a person's sexual characteristics, such as external and internal genitalia, hormonal characteristics, and secondary sexual characteristics. **Sexual orientation** is based on a person's choice of a love object: heterosexual (opposite sex), homosexual (same sex), bisexual (both sexes), or asexual (no sex).

Gender identity is based on a person's sense of maleness or femaleness; it is established by age 3. **Gender role** is based on the external behavioral patterns that reflect a person's inner sense of gender identity.

MASTURBATION

Masturbation is a normal precursor of object-related sexual behavior. All men and women masturbate.

- Genital self-stimulation begins in early childhood.
- As puberty arrives, sexual interest peaks and masturbation increases.
- Adolescents and adults typically have sexual fantasies while masturbating.
- Commonly seen among adolescents, married couples, and the elderly
- Excessive only if it interferes with daily functioning

HOMOSEXUALITY

Homosexuality was removed from the DSM in 1980 as a mental illness. It is considered a variant of human sexuality, not a pathologic disorder.

- Most homosexuals report feelings toward same-sex individuals since adolescence.
- Recent studies indicate it may be due to genetic and biologic causes.
- Greater incidence among monozygotic versus dizygotic twins
- No difference in the sexual practices from those exhibited by heterosexuals

- Male–male relationships may be less stable than female–female relationships.
- Equal incidence of mental illness when compared with heterosexuals.
- Exceptions (normal during adolescence):
  - Visual comparison of genitalia
  - Mutual masturbation
  - Group exhibitionism
  - Handholding, kissing, etc.

SEXUAL DYSFUNCTIONS

A group of disorders related to a particular phase of the sexual response cycle. These disorders can be psychologic, biologic, or both, and include, desire, arousal, orgasm, and pain.

Table I-16-1. Sexual Dysfunctions

Phase	Characteristics	Disorder	Treatment
Desire	Focuses on the patient's drives, motivation, and desires	**Hypoactive sexual desire:** patients have a decrease or absence of sexual fantasies, desires, etc. **Sexual aversion:** a complete aversion to all sexual contact	Address issues with patient, such as feelings of guilt, poor self-esteem, homosexual impulses, etc. Couples therapy may be indicated if due to marital conflict.
Arousal	Consists of a sense of sexual pleasure with accompanying physiologic changes	**Female sexual arousal:** persistent failure to achieve or maintain adequate lubrication during the sexual act **Impotence:** persistent or recurrent inability to attain or maintain adequate erection until completion of the sexual act	Address issues of guilt, anxiety, and fear. Evaluate for use of medications that cause vaginal dryness, such as antihistamines or anticholinergics. Instruct in relaxation techniques. Must rule out if organic versus psychological. Consider plethysmography or postage stamp test.
Orgasm	Physiologic state in which sexual tension is released and contractions are produced in various organs.	**Female orgasmic disorder and delayed ejaculation:** recurrent or persistent inability to achieve an orgasm either through masturbation or sexual intercourse **Premature ejaculation:** ejaculation before the man wishes to do so, before penetration, or just after penetration	Address issues of guilt, fear of impregnation, etc. Treatment includes use of vibrators, education, and fantasy. Consider behavioral techniques such as squeeze and stop-and-go. Address issues of anxiety about the sexual act. Consider the use of SSRIs to delay ejaculation.
Pain	Subjective sense of pain associated with the sexual act. Most likely due to dynamic factors.	**Genito-pelvic pain disorder:** Pain associated with sexual intercourse in either male or female. Not diagnosed when organic cause has been found or if due to lack of vaginal lubrication. **Penetration disorder:** involuntary constriction of the outer one-third of the vagina that interferes with the sexual act	Help the woman deal with issues of anxiety and tension about the sexual act. Behavioral techniques, such as the use of dilators and relaxation. Address issues of fear of impregnation, strict upbringing, religion, etc.

PARAPHILIC DISORDER

A 20-year-old man was caught outside his neighbor's window, looking in as she disrobed. Before his arrest, he would wander the subway stations and rub himself up against women as well as expose himself to women who were nearby. All of these activities produced sexual pleasure in the patient.

Definition. A group of disorders that is recurrent and sexually arousing. Usually focus on humiliation and/or suffering and the use of nonliving objects and involve nonconsenting partners. Typically occur for >6 months and are usually distressing and cause impairment in patient's level of functioning.

Risk Factors/ Epidemiology. Affects men more than women. Peak incidence is age 15–25. Tend to have other paraphilias, and as the patient ages the frequency decreases.

Physical and Psychiatric Presenting Symptoms

- Sexual activity is ritualistic.
- Fantasy is typically fixed and shows very little variation.
- Intense urge to carry out the fantasy

Treatment. Individual psychotherapy is indicated to help the patient understand the reasons why the paraphilia developed. Patient also becomes aware of daily activities and how they are related to the paraphilic behavior. Behavioral techniques, such as aversive conditioning, may be indicated in some situations. Pharmacotherapy consists of antiandrogens or SSRIs to help reduce patient's sexual drive.

Differential Diagnosis. Must distinguish between experimentation and actual paraphilias

Types of Paraphilic Disorders

- **Exhibitionism:** recurrent urge to expose oneself to strangers
- **Fetishism:** involves the use of nonliving objects usually associated with the human body
- **Frotteurism:** recurrent urge or behavior involving touching or rubbing against a nonconsenting partner
- **Pedophilia:** recurrent urges or arousal toward prepubescent children. Most common paraphilia.
- **Voyeurism:** recurrent urges or behaviors involving the act of observing an unsuspecting person who is engaging in sexual activity, disrobing, etc. Earliest paraphilia to develop.
- **Masochism:** recurrent urge or behavior involving the act of humiliation
- **Sadism:** recurrent urge or behavior involving acts in which physical or psychologic suffering of a victim is exciting to the patient
- **Transvestic fetishism:** recurrent urge or behavior involving cross-dressing; usually found in heterosexual men

GENDER DYSPHORIA

> Billy, a 5-year-old boy, was found in his parent's bedroom wearing his mother's clothes. He has been observed going to the bathroom to urinate while sitting on the toilet as well as playing with dolls instead of his trucks and guns. He prefers to wear dresses and hates being a boy.

Definition. Also called gender identity dysphoria. A disorder characterized by a persistent discomfort and sense of inappropriateness regarding the patient's assigned sex.

Risk Factors/Epidemiology. Seen more frequently in men than in women. Cause is unknown. Many believe it may be due to biologic reasons, such as hormones, etc.

Physical and Psychiatric Presenting Symptoms

- Children will have preference for friends of the opposite sex.
- Preoccupied with wearing opposite gender's clothes
- Refuse to urinate sitting down, if a girl, or standing up, if a boy
- Believe they were born with the wrong body
- Routinely request medications or surgery to change their physical appearance
- Women may bind their breasts, have mastectomies, take testosterone to deepen the voice.
- Men may have electrolysis to remove body hair, may take estrogens to change the voice, and may have surgeries to remove the penis and create a vagina.

Practice Questions

1. What is the treatment of choice for premature ejaculation?
   (A) Plethysmography
   (B) Dilators
   (C) Squeeze technique
   (D) Postage stamp
   (E) Aversive conditioning

2. What is the most common cause of erectile dysfunction due to a medical condition?
   (A) Pancreatitis
   (B) Diabetes
   (C) Cirrhosis
   (D) Myocardial infarction
   (E) UTI

1. **Answer: C.** The treatment of premature ejaculation typically consists of behavioral techniques aimed at prolonging the time before ejaculation occurs. These include the squeeze-and-go technique. Choices A and D are for the diagnosis of erectile dysfunction. Choice B is for the treatment of pain/penetration disorder.
2. **Answer: B.** Diabetes has been known to be a common cause of erectile dysfunction. Alcohol has been proven to be a common cause of erectile dysfunction in men of all ages.

Psychopharmacology 17

Learning Objectives

- ❑ Describe the classes of drug, mechanism of action, and common adverse effects of typical antipsychotic, atypical antipsychotic, antidepressant, mood-stabilizing, and anxiolytic medications
- ❑ Describe the indications and procedural steps for electroconvulsive therapy

ANTIPSYCHOTIC MEDICATION

Antipsychotic medications (APMs) are used to treat manifestations of psychosis and other psychiatric disorders. The precise mechanism of action is unknown; however, APMs block several populations of dopamine (D2, D4) receptors in the brain. The newer APMs also block some serotonin receptors (5HT), a property that may be associated with increased efficacy.

APMs also variably block central and peripheral cholinergic, histaminic, and alpha-adrenergic receptors.

Typical Antipsychotic Medications

Typical antipsychotics such as haloperidol were developed in the 1950s to treat psychosis.

- Work mostly on dopamine receptors
- Treat positive symptoms (hallucinations and delusions)
- Have many side effects (haloperidol, fluphenazine, chlorpromazine, etc.)

Atypical Antipsychotic Medications

Newer, atypical antipsychotic medications are now always used as first-line agents (risperidone, olanzapine, etc.).

- Work mostly on dopamine and serotonin receptors
- Treat both positive and negative symptoms (flat affect, poor grooming, social withdrawal, anhedonia)
- Have fewer side effects

Side Effects

There are several general groups of side effects with antipsychotic medications.

- **Sedation,** due to antihistaminic activity
- **Hypotension,** due to alpha-adrenergic blockade; most common with low-potency APMs

- **Anticholinergic symptoms:** dry mouth, blurred vision, constipation, urinary retention, flushed skin, delirium
  - Effects may be additive if given with other anticholinergics.
  - Block parasympathetic receptors
  - Avoid in the elderly
- **Endocrine symptoms:** gynecomastia, galactorrhea, amenorrhea
- **Dermal and ocular symptoms:** photosensitivity, abnormal pigmentation, cataracts
- **Cardiac conduction abnormalities** (especially with thioridazine), agranulocytosis with clozapine
- **Movement-related symptoms**
  - **Acute dystonia (dystonic reaction)**
    - Presents as spasms of various muscle groups
    - Can be dramatic and frightening to patient, a potential contributing factor to subsequent noncompliance with treatment
    - Young men may be at higher risk, seen in 10% patients.
    - Treatment is anticholinergics, such as benztropine, diphenhydramine, and trihexyphenidyl
    - Can occur within hours after treatment with antipsychotic medication
  - **Akathisia**
    - Presents as motor restlessness, "ants in your pants"
    - Differential diagnosis: often mistaken for anxiety and agitation
    - Treatment is a lower dosage or switching to another antipsychotic medication; adding benzodiazepines or beta-blocker
    - Can occur several weeks after treatment with antipsychotic medication
  - **Tardive dyskinesia (TD)**
    - Presents as choreoathetosis and other involuntary movements; movements often first involve the tongue or fingers and later involve the trunk
    - Etiology may be a "chemical denervation hypersensitivity" caused by chronic dopamine blockade in basal ganglia
    - Patients who take high doses of older antipsychotic medication for long periods of time are at highest risk, and movements gradually worsen with continued use
    - Seen more frequently in elderly women
    - Treatment is switching to a newer antipsychotic medication
    - Can occur after 3–6 months after treatment with antipsychotic medication
- **Neuroleptic malignant syndrome** (primary adverse effect of antipsychotic medication use)
  - Rare but potentially life-threatening
  - Presents as muscular rigidity, hyperthermia, autonomic instability, and delirium
  - CPK will be elevated.
  - Usually associated with high dosages of high-potency antipsychotic medication
  - Treatment is immediate discontinuation of the medication and physiologic supportive measures; dantrolene or bromocriptine may be used

Treatment of psychotic symptoms is an atypical agent (**first-line**).

Table I-17-1. Atypical Antipsychotic Medications

Medication	Indications/Side Effects
Clozapine (gold standard for treatment of schizophrenia)	• Not used as first-line agent • May cause agranulocytosis (<1%) so essential to monitor WBC
Risperidone	• Increased risk of movement disorders • Elevated prolactin
Paliperidone (active metabolite of risperidone)	• Fewer side effects than risperidone
Olanzapine	• Weight gain • Metabolic syndrome • Diabetes
Quetiapine	• Lowest risk of movement disorders
Ziprasidone	• Prolonged QT interval
Aripiprazole	• Partial dopamine agonist at low doses • May be used as adjunct for depression
Asenapine	• Sedation • Akathisia
Iloperidone	• Hypotension • Dizziness • Somnolence
Lurasidone	• Somnolence • Akathisia • Weight gain

ANTIDEPRESSANT (AD) MEDICATIONS

The overall efficacy for treatment of major depressive disorder is around 70%. It is difficult to predict individual response, so various trials may be needed before an effective one is found.

- Consider newer ADs first because of better safety profile.
- Medications differ greatly in their side-effect profile, so consider patient preference and ability to tolerate.
- Older antidepressants are extremely dangerous when an overdose is ingested.
- When used to treat depressive symptoms, prescribe in small quantities and only after determining the absence of suicidal intent.
- If no response to treatment after 4 weeks or if patient cannot tolerate current antidepressant, switch to another.
- Continue treatment 6 mos to 1 yr after favorable response.

Note

Atypical agents are always first-line for psychotic symptoms.

- **In the ED**: short-acting intramuscular agent such as haloperidol, fluphenazine, olanzapine, ziprasidone
- **For nonadherence**: long-acting antipsychotic medication such as haloperidol, fluphenazine, risperidone, paliperidone, olanzapine
- **As a last resort**: clozapine
- **If all meds ineffective**: consider ECT

- Older antidepressants are extremely dangerous when an overdose is ingested. When used to treat individuals with depressive symptoms, clinicians should generally prescribe in small quantities and only after determining the absence of suicidal intent.
- If no response to treatment after 4 weeks, or if patient cannot tolerate current antidepressant, switch to another.
- Treatment should continue for 6 months to 1 yr after favorable response.

Untoward effects

- **Sedation:** due to histamine blockade
- **Hypotension:** due to alpha blockade
- **Anticholinergic effects:** dry mouth, blurry vision, urinary retention, confusion
- **Cardiac:** conduction abnormalities most marked with TCAs
- **Seizures:** bupropion
- **Sexual dysfunction:** anorgasmia and decreased libido with SSRIs; priapism with trazodone

SSRIs

Inhibit reuptake of serotonin

- **Types:** Fluoxetine, paroxetine, and sertraline, fluvoxamine, citalopram, escitalopram
- Reduced number of serious side effects
- Simple dosing schedules
- Significant incidence of agitation, nausea/vomiting, headache, diarrhea, sexual dysfunction

"Hybrid" Antidepressants

- Venlafaxine: inhibits reuptake of NE and S, used for depression and anxiety, may cause hypertension, blurry vision, diaphoresis, etc.
- Desvenlafaxine: inhibits reuptake of NE and S, active metabolite of venlafaxine therefore fewer side effects
- Duloxetine: inhibits reuptake of NE and S, approved for depression and neuropathic pain
- Bupropion: inhibits reuptake of NE and dopamine, approved for depression and smoking cessation; may cause seizures so avoid using in patients with eating disorders, alcohol withdrawal seizures, or seizure disorders
- Trazodone: S agonist and reuptake inhibitor, approved for depression and insomnia; may cause priapism (prolonged and painful erection)
- Mirtazapine: classified as tetracyclic antidepressant, approved for depression and insomnia; weight gain is main side effect

TCAs

- Inhibit reuptake of NE, S, and dopamine
- Include nortriptyline, amitriptyline, imipramine, desipramine, clomipramine, etc.
- Adverse effects: (especially tertiary TCAs) significant sedation, orthostatic hypotension, and anticholinergic effects. They are the most dangerous antidepressants in overdose.

MAOIs

MAOIs inhibit MAO-A and/or MAO-B in the CNS and have antidepressant efficacy. They differ by their type of inhibition (reversible or irreversible), severity of side effects, and specificity of inhibition (MAO-A or -B).

- Include phenelzine, tranylcypromine, and isocarboxazid
- **Selegiline:** selective inhibitor of MAO-B; currently approved only for treatment of Parkinson's disease
- **Indications:** second-line treatment for major depressive disorder, depressive disorders with atypical features, and some anxiety disorders
- **Hypertensive crisis:** may occur with tyramine-rich foods or if certain other medications are ingested, e.g., nasal decongestants, antiasthmatics, and amphetamines. Avoid red wine, aged cheese, and chocolate.
- **Adverse effects:** sedation, weight gain, orthostatic hypotension, liver toxicity (with hydrazine MAOIs), and sexual dysfunction

ELECTROCONVULSIVE THERAPY (ECT)

Indications

- Major depressive episodes that have not responded to antidepressant medication or mood stabilizers
- Major depressive episodes with high risk for immediate suicide
- Major depressive episodes when antidepressant medication is contraindicated
- Major depressive episodes in patients who have responded well to ECT in the past

Untoward effects and contraindications

- Transient memory disturbance: increases in severity over the course of ECT and then gradually resolves over several weeks
- Complications of associated anesthesia and induced paralysis
- Transiently increased intracranial pressure (thus, use extreme caution with any space-occupying intracranial lesions)

MOOD-STABILIZING MEDICATIONS

Lithium

Indications

- Bipolar and schizoaffective disorders: first-line medication for treatment and prophylaxis of mood episodes
- Adjunctive treatment of major depressive disorder: may augment responsiveness to antidepressant medications in some patients

Untoward Effects

- Dose-related: tremor, gastrointestinal (GI) distress, headache
- Dermatologic problems: acne; interferes with patient compliance
- Weight gain: may interfere with patient compliance
- Cardiac conduction: electrocardiogram (ECG) changes usually benign
- Hypothyroidism: 5% of patients develop thyroid problems
- Leukocytosis: usually occurs and seems to be benign
- Polyuria: diabetes insipidus is common and may be troublesome to patients
- Teratogenicity: associated with cardiac abnormalities; contraindicated in first trimester, Ebstein's anomaly (tricuspid valve)
- Nephrotoxic

Toxicity Management

- Keep plasma levels <1.5 mEq/L; optimal 1.0 mEq/L
- Dehydration and hyponatremia predispose to lithium toxicity by increasing serum lithium levels. Lithium may increase with ACE inhibitors, NSAIDs, loop and thiazide diuretics.
- Tremor at therapeutic levels may respond to decreased dosage.

Divalproex

- Treatment of choice for rapid-cycling bipolar disorder or when lithium is ineffective, impractical, or contraindicated.
- Increasingly popular in emergency settings, may give loading dose
- Time course of treatment response is similar to lithium.
- Efficacy for prophylaxis is unclear.
- Untoward effects: sedation, cognitive impairment, tremor, GI distress, hepatotoxicity, weight gain, possible teratogenicity (spina bifida), and alopecia.

Carbamazepine

- Second-line choice for treatment of bipolar disorder when lithium and divalproex are ineffective or contraindicated
- Rare but serious hematologic and hepatic side effects and significant sedation make carbamazepine less useful.
- May cause agranulocytosis

Lamotrigine

- Approved for bipolar depression
- May cause Steven-Johnson syndrome

ANXIOLYTIC MEDICATIONS

There are 2 types of anxiolytic medications: **benzodiazepines**, which facilitate transmission of GABA, and **buspirone**, which is an S receptor partial agonist.

Benzodiazepines

- Do not mix with alcohol or other sedative-hypnotic medications.
- Consider dependency-potential.
- Use lower dosages for the elderly; may cause confusion, problems with memory, and falls.
- Abrupt discontinuation may cause seizures.

Buspirone

- Effective for generalized anxiety disorder and social phobia
- Lag time of about 1 week before clinical response
- No additive effect with sedative-hypnotics
- No sedation or cognitive impairment but may cause headache
- No withdrawal syndrome

18 Suicide

Learning Objectives

- ❑ Describe the epidemiology and biological indicators associated with suicide and suicidal gestures
- ❑ Describe the steps required to evaluate a patient's risk of suicide

SUICIDE

Presentations

- Recent suicide attempt
- Complaints of suicidal thoughts
- Admission of suicidal thoughts upon questioning
- Demonstration of possible suicidal behavior

Risk Factors for Suicidal Behavior

- History of suicide threats and attempts
- Perceived hopelessness (demoralization)
- Presence of psychiatric illness/drug abuse
- Males
- Elderly
- Social isolation
- Low job satisfaction
- Chronic physical illness

Emergency Assessment

- Detain until the emergency evaluation is completed
- Take all suicide threats seriously
- Question about suicide ideation, intent, and plan
- Get information from third parties
- Don't identify with the patient
- Emergency treatment decisions about suicidal behavior are based on clinical presentation and presence of risk factors.

19 Psychotherapies

Learning Objectives

- ❑ Describe and compare the major forms of psychotherapy and behavioral therapy used in practice today

Table I-19-1. Psychotherapies

Type of Therapy	Goal	Selection Criteria	Duration	Techniques
Psychoanalysis	Resolution of neurosis	Psychologically minded	4–5× per week for years	Free association, defense analysis, interpretation of transference
Insight oriented	Focus on interpersonal goals	Intact reality testing, capacity for insight	1–3× per week for months to years	Defense analysis, interpretation of transference
Supportive	Support reality testing, provide ego support	Healthy patients in time of crises or very ill patients	Days to months to years	Problem solving, suggestion, reinforcement
Behavioral	Modify learned behavior patterns	Those with maladaptive behaviors or psychophysiologic disorders	Time limited	Relaxation techniques, aversive therapy, systematic desensitization, flooding, token economy
Group	Alleviation of symptoms, change relationships, alter family-couple dynamics	Groups target specific disorders, family and couples, personality disorders, etc.	1× per week for weeks to years	Group specific
Cognitive	Change distorted views of self, world, and others	Depressive disorders	1× per week for 15–25 weeks	Assigned readings, homework, behavioral techniques, identification of irrational beliefs and attitudes

PART II

Epidemiology & Ethics

Epidemiology 20

Learning Objectives

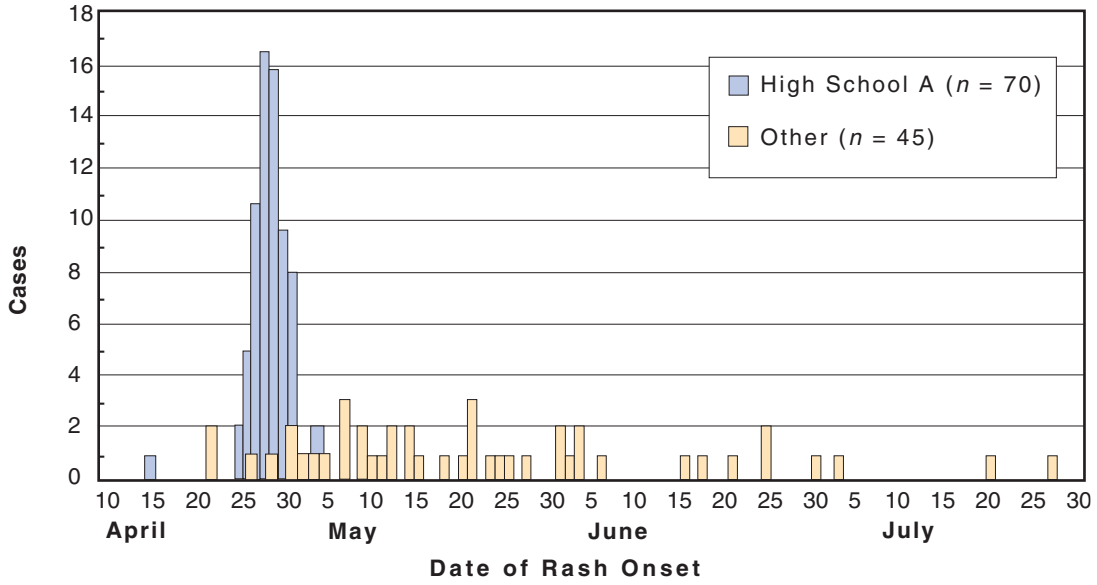
- ❑ Define incidence, prevalence, specific rates, adjusted rates, and other statistical measures, as they relate to morbidity and mortality
- ❑ Perform survival analysis including accounting for potential life lost
- ❑ Describe the types of prevention
- ❑ Show how prevalence, sensitivity, and specificity relate to the value of screening tests
- ❑ Answer questions about study design and bias in research

OVERVIEW

Epidemiology is the study of the distribution and determinants of health-related states within a population. It refers to the patterns of disease and the factors which influence those patterns.

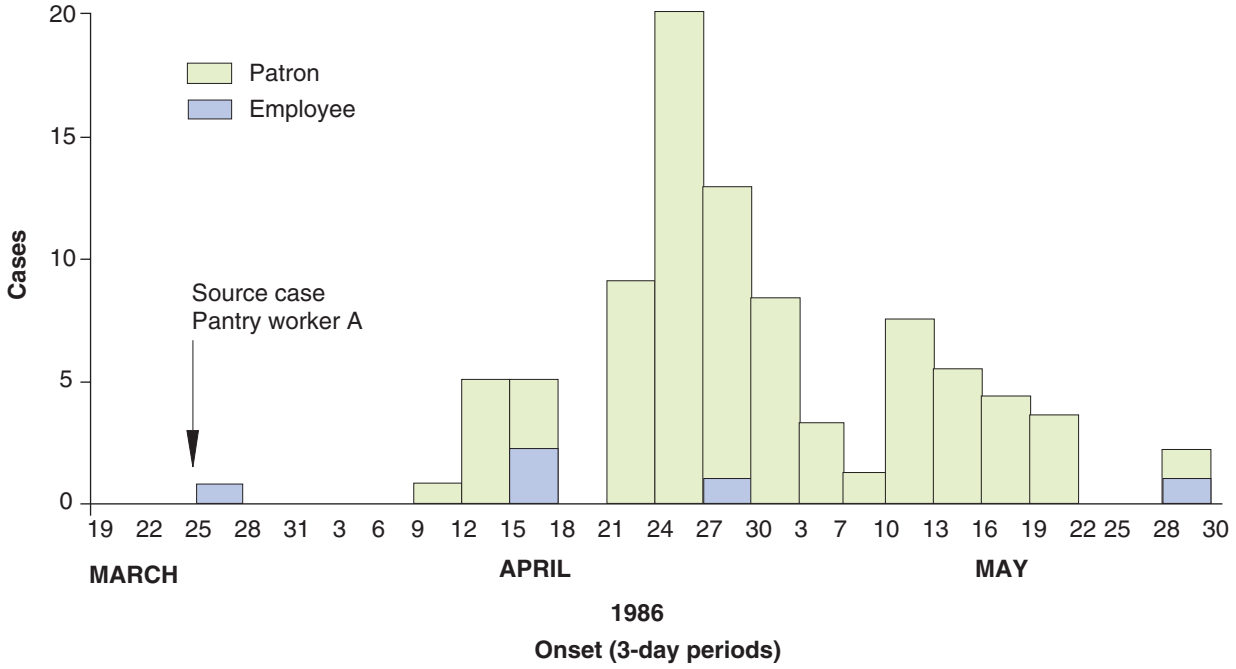
- **Endemic:** The usual, expected rate of disease over time; the disease is maintained without much variation within a region.
- **Epidemic:** Occurrence of disease in excess of the expected rate; usually presents in a larger geographic span than endemics (**epidemiology** is the **study of epidemics**).
- **Pandemic:** worldwide epidemic
- **Epidemic curve:** Visual description (commonly histogram) of an epidemic curve is disease cases plotted against time; classic signature of an epidemic is a **"spike" in cases during a period of time**.

Incubation period is the period of time from the point of infection to the onset of clinical illness.



Reported measles cases by date of rash onset, Elgin, Illinois, April 15 to July 28, 1985

Figure II-20-1. Measles Outbreak



Onsets of illness in patrons and employees: hepatitis A outbreak on a floating restaurant, Florida.

Figure II-20-2. Food-Borne Outbreak

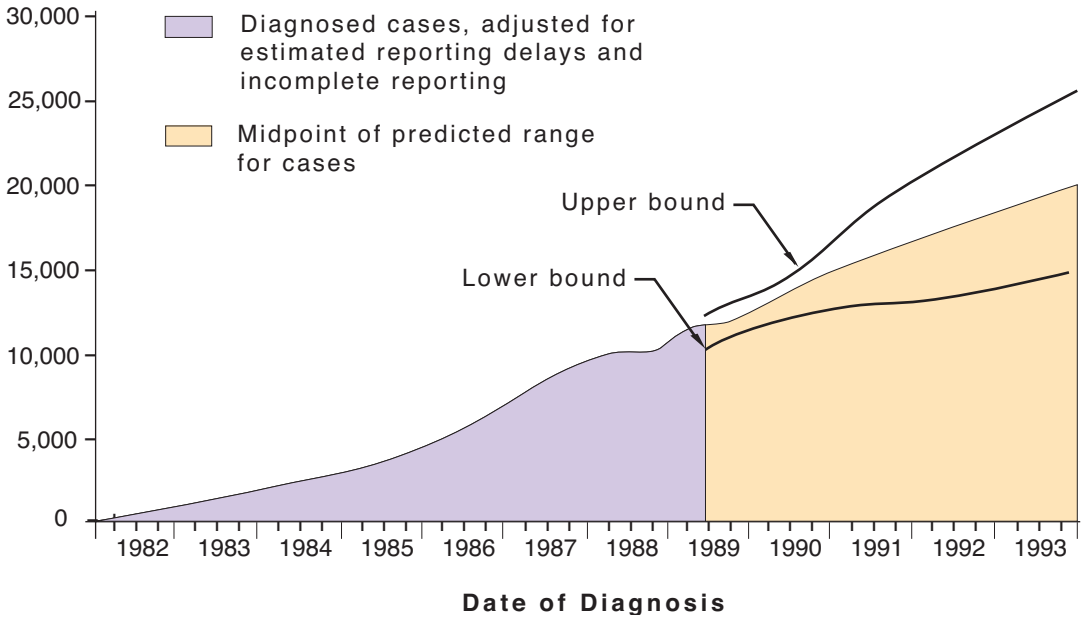


Figure II-20-3. Multiple-Year Increase in AIDS Cases in the United States

Health service interventions are evaluated using the following concepts/metrics:

- **Efficacy:** performance of an intervention under optimal conditions, e.g., prophylactic medications in a clinical trial
- **Effectiveness:** actual results in the real world, e.g., treatment outcomes in the community
- **Efficiency:** a ratio of the benefit compared to the cost associated with an intervention (high efficiency would deliver a greater benefit at minimal cost)

Upper and lower bounds account for uncertainty of the estimate (most commonly 95% confidence intervals).

TYPES OF PREVENTION

The goals of prevention in medicine are to promote health, preserve health, restore health when it is impaired, and minimize suffering and distress. These goals aim to minimize both morbidity and mortality.

- **Primary prevention** is the promotion of health at both individual and community levels; this is done by facilitating health-enhancing behaviors, preventing the onset of risk behaviors, and diminishing exposure to environmental hazards. **Primary prevention efforts decrease disease incidence.**
- **Secondary prevention** is the screening for risk factors and early detection of asymptomatic or mild disease, permitting timely and effective intervention and curative treatment. **Secondary prevention efforts decrease disease prevalence.**
- **Tertiary prevention** is the reduction of long-term impairments and disabilities and prevention of repeated episodes of clinical illness. The goals of tertiary prevention are to prevent recurrence and slow progression.

Note

- **Prevalence** is the proportion of population affected by a disease (disease burden).
- **Resource allocation** is often directed at disease prevalence.

Primordial prevention is a newer concept in disease prevention. It targets the most distal determinants of health (social, economic, environmental, and cultural).

Some examples of **prevention for cardiovascular disease** are as follows:

- **Primary prevention:** health education programs to promote healthy lifestyle and prevent onset of heart disease risk factors, e.g., Hearty Heart nutrition program for elementary school children or smoking cessation program
- **Secondary prevention:** community screening for blood pressure, peripheral artery disease
- **Tertiary prevention:** graded aerobic physical activity program prescribed to patients during recovery from first myocardial infarction

Practice Questions

Response options for Questions 1–4:

A. Quaternary prevention
B. Primary prevention
C. Secondary prevention
D. Tertiary prevention
E. Palliative care

1. Breast self-examination
2. Physical therapy/rehabilitation and ergonomic training program for blue-collar workers recovering from severe back strain injury sustained on the job
3. School-based sexual health education program for middle school students
4. Confidential PPD testing to detect latent TB infection conducted at community clinics by county health department personnel

1. **Answer: C**. Self-screening for early detection leading to early diagnosis and effective, life-saving treatment.
2. **Answer: D**. Rehabilitation following an episode of injury with a concurrent focus on preventing subsequent injury.
3. **Answer: B**. Prevention of onset of risky sexual behaviors.
4. **Answer: C**. Screening to detect TB infection, to be followed by therapy to prevent progression to active TB.

Practice Questions

Response options for Questions 5–7:

A. Hypoendemic
B. Endemic
C. Epidemic
D. Hyperendemic
E. Pandemic

5. Multinational outbreak of influenza
6. Rapid rise in AIDS cases among drug injectors in Bangkok in the late 1980s
7. Long-term, relatively constant rate of occurrence of colorectal cancer in U.S. women

5. **Answer: E**. A pandemic is an epidemic that crosses national borders.
6. **Answer: C**. AIDS appeared suddenly, and the epidemic increased exponentially.
7. **Answer: B**. When disease cases are plotted over time, a flat horizontal line depicts an endemic pattern.

MEASURES OF MORBIDITY AND MORTALITY

Rate

Rate is the frequency of occurrence of epidemiologic events in populations. It is used to compare epidemiologic events among populations.

- Rates allow direct comparisons of "events per identical number of people" in 2+ populations.
- Rates permit comparisons of epidemiologic events occurring in a single population assessed at several points in time.

The rate equation is:

$$\text{Rate} = \frac{\text{Numerator}}{\text{Denominator}} \times \text{Multiplier}$$

where the **numerator** is the number of **epidemiologic events**, the **denominator** is the number of **people in the population of interest**, and the **multiplier** is selected so that the **result of the rate computation generally yields a number from 1–100** (rather than a decimal).

- For **major vital statistics**, such as birth rate, death rate, and infant mortality rate, the preferred multiplier is 1,000. The result is expressed as a **rate per 1,000.**
- For **individual diseases**, the most common multiplier is 100,000. The result is expressed as a **rate per 100,000.**

It is **essential** that the **numerator units are matched with the denominator**. Match on person, place, and time characteristics.

$$\text{Rate} = \frac{\text{Epidemiologic events occurring in a population of persons at a given place at a given time}}{\text{Defined population of persons at a given place at a given time}} \times \text{Multiplier}$$

SPECIFIC AND ADJUSTED RATES

Specific Rates

Specific rates **specify a subset of the total population** that is singled out for special examination or comparison with other subsets of the population. Use the following formula:

$$\text{Specific rate} = \frac{\text{All events in specified subpopulation}}{\text{Specified subpopulation}} \times \text{Multiplier}$$

Common demographic variables used for specific rates are age group, gender, race/ethnicity, highest level of education attained, marital status, and socioeconomic status. Populations can be stratified on 2+ demographic variables at a time.

Matching the numerator and denominator is the most important concept for computing a specific rate. For example:

"Event" of interest:	Cancer deaths
Place:	State of Nevada
Time:	Calendar year, 2006
Rate of interest:	Age-specific rate (rate for a specified age group) for ages 45–64
Formula:	$\frac{\text{Deaths from cancer among persons ages 45–64 in Nevada during 2006}}{\text{Population of Nevada residents ages 45–64, midyear 2006}} \times 100{,}000$

Adjusted Rates (or Standardized)

Adjusted rates are rates calculated after using statistical procedures, in order to minimize demographic differences between populations being compared. Comparisons of rates between 2 groups may be misleading if the composition of the groups differs on important demographic characteristics.

Adjustment improves the validity of the comparison, when there is an imbalance of risk factors among 2 populations. In the following example, rate adjustment is clearly essential.

> In the same city, the rate of alcoholism and alcohol abuse is found to be higher among workers in an automobile assembly plant compared with same-age workers at a textile mill.

Adjustment for gender differences is warranted. First, the **2 populations differ on a demographic characteristic**: Automotive workers tend to be men; textile workers tend to be women. Second, the **disorder is related to the same demographic**: Alcohol problems are more prevalent in men. The higher observed rate in automotive workers may be due to the marked differences in gender in the 2 employee populations.

> In the same company, the rate of lung cancer is found to be higher among male factory workers age 50–64 than among male computer programmers age 50–64.

Adjustment for level of education is warranted. First, the 2 populations differ on a demographic characteristic: Factory workers tend to have a low level of education; computer programmers are likely to be college graduates. Second, the disease/disorder is related to the same demographic. The major cause of lung cancer is cigarette smoking. People with lower levels of education have higher smoking rates; college graduates have the lowest smoking rates. The differences in lung rates may reflect expected differences in smoking prevalence rates for workers with different levels of education.

Properties of a board-style adjusted rate problem:

- A significant difference in the rate of disease is declared to exist between 2 groups. The compared rates are unadjusted.
- The groups differ on a key demographic variable.
- The disease is known to be related to the same demographic variable.
- Adjustment will tend to make the observed difference between unadjusted rates disappear.

Table II-20-1. Disease Rates Positively Correlated with Age

		Population A		Population B		Population C	
	Disease Rate by Age Group	Cases	Population	Cases	Population	Cases	Population
Younger	1/1,000	1	1,000	2	2,000	3	3,000
Intermediate	2/1,000	4	2,000	4	2,000	4	2,000
Older	3/1,000	9	3,000	6	2,000	3	1,000
		14	6,000	12	6,000	10	6,000
Crude Rates	Per/1,000	2.3		2.0		1.6	

Practice Questions

8. In the United States, the crude (unadjusted) suicide rate for physicians is significantly higher than it is for the general population. What is the most appropriate interpretation of this finding?

   A. Higher suicide rates in physicians are likely to be related to job stress, including life-and-death decision making for patients in the care of the physician.
   B. Higher rates of suicide in physicians are likely to be related to constant exposure to human suffering, trauma, and death.
   C. Physicians have higher rates of suicide than the general population; no further interpretation is possible from the information presented.
   D. While the unadjusted rate of suicide is higher for physicians, failure to adjust for differences between physicians and the general population on socioeconomic status precludes meaningful interpretation of this finding.
   E. The finding of statistical significance proves that physicians are at higher risk for suicide than nonphysicians.

8. **Answer: D**. When a significant relationship is stated but the comparison groups have some obvious demographic difference, look for the answer that suggests conclusions may be invalid unless rates are adjusted to compensate for those differences. Here, physicians are generally a higher socioeconomic status (SES) group relative to the general population. Suicide rates are elevated for high-SES people. Once adjusted for SES differences, the finding of higher suicide rates in physicians no longer stands.

MEASURES OF MORBIDITY

Prevalence and Incidence

Prevalence is the number of individuals with a disease divided by the total number of individuals in a population. This can be measured at one point in time (point prevalence) or as the proportion of individuals who had the disease during a time period of interest (period prevalence). A chronic condition such as hypertension or diabetes tends to carry a high prevalence in the population, because once someone acquires it he is not usually cured of it.

The numerator refers to **all individuals** who have the illness at the time(s) in question.

$$\text{Prevalence} = \frac{\text{Persons with existing disease at a given place at a given time}}{\text{Population of persons at risk for disease at a given place at a given time}} \times \text{Multiplier}$$

The **incidence** rate is the rate of new disease events in a population at risk during a period of time. It can be calculated only over a period of time, not at a single point.

$$\text{Incidence rate} = \frac{\text{Persons with disease onset at a given place during a specified period of time}}{\text{Population of persons at risk for the disease at a given place during a specified period of time}} \times \text{Multiplier}$$

Note

(Conceptual) Relationship between Incidence and Prevalence:

- Prevalence = Incidence × Duration
- $\text{Duration} = \frac{\text{Prevalence}}{\text{Incidence}}$
- Changes in incidence, duration, or both will ultimately affect prevalence.

When calculating incidence rate, note that **those who already have a given disease are not included** in the population at risk.

Attack rate is a type of incidence rate that focuses on a known exposure or risk. If 10 of 100 children who attend daycare A and 40 of 100 children who attend daycare B develop diarrhea, the attack rate would be 10% for attendance at daycare A and 40% for attendance at daycare B.

Prevalence Pot

A "prevalence pot" is often used to understand prevalence and its relationship to incidence. At the first moment of observation, the count of cases "in the pot" provides an estimate of point prevalence. Incident cases are observed over time. These new cases are added to the pre-existing cases. As long as clinical illness persists, cases remain in the pot.

Prevalence **can be estimated when disease incidence and duration are known**:

$$\text{Prevalence} = \text{Incidence} \times \text{Duration (conceptual formula only)}$$

A disease may have low incidence but long duration, causing prevalence to be higher.

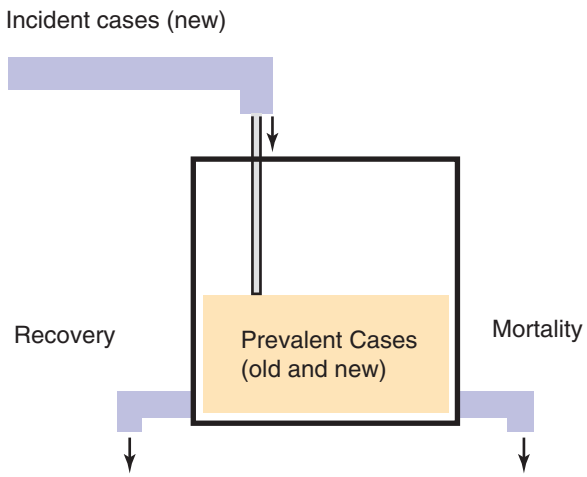


Figure II-20-4. Prevalence Pot Diagram

Cases leave the prevalence pot in one of 2 ways: recovery or death. Changes in prevalence over time can be determined by **monitoring trends in incidence, recovery, and death**.

The **factors affecting prevalence** are as follows:

Increase

- Increase in incidence cases, e.g., improved screening methods
- Longer disease duration, e.g., diabetes
- Better treatment of disease, which results in patients with chronic illness but not "cured," e.g., diabetics

Decrease

- Decrease in incidence cases, e.g., vaccination program
- Shorter disease duration, e.g., high case fatality rate
- Improved treatment of disease, which results in "cured" patients

Practice Questions

9. A pharmaceutical company completes trials on a vaccine for a severe strain of influenza virus demonstrating high vaccine efficacy. The FDA approves the vaccine for use in the United States. As the influenza pandemic approaches U.S. borders, the CDC launches a campaign to vaccinate the population using local public health department personnel throughout the country to ensure the vaccine is available, free of charge, to all people. Assuming a high degree of vaccine coverage is achieved, what is the expected impact of this major public health initiative?

   A. Decreased duration of influenza illness leading to decreased prevalence
   B. Decreased incidence of influenza illness leading to decreased prevalence
   C. Decreased incidence offset by increased duration: no change in prevalence
   D. No change in observed incidence or duration: no change in prevalence
   E. Effects on prevalence cannot be determined from the information provided

10. A new, effective treatment for a common disease, leading to complete cure, is developed. Which of the following impacts on disease occurrence is expected?

   A. Decreased duration of illness, leading to decreased prevalence
   B. Decreased incidence of illness, leading to decreased prevalence
   C. Decreased incidence and duration of illness, leading to decreased prevalence
   D. No change in observed incidence or duration: no change in prevalence
   E. Effects on prevalence cannot be determined from the information provided

11. Which term is used when cost/benefit ratio analysis is used to evaluate public health service interventions?

   A. Efficacy
   B. Effectiveness
   C. Efficiency
   D. Equity
   E. None of the above

9. **Answer: B**. Vaccination decreases the likelihood of development of new infection and clinical disease. In turn, the prevalence during the peak of the influenza season will be decreased. Efficacy reflects how well an intervention performs under ideal circumstances.

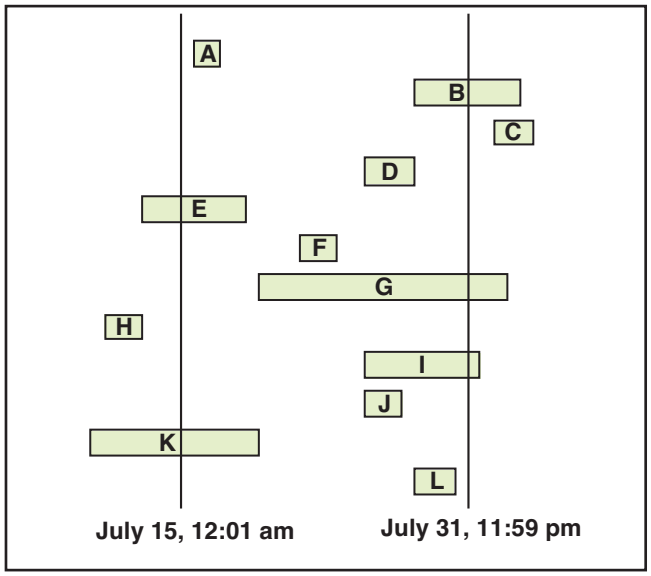
10. **Answer: A**. An effective treatment will move people more quickly toward recovery. Average duration of illness will decrease. Prevalence–the proportion of people ill with the disease at a point in time–will also decrease. This will apply to both acute and chronic diseases. Effectiveness refers to how well an intervention performs in real conditions. Under ideal circumstances, some interventions are relatively efficacious, but less effective in reality.

11. **Answer: C**. Efficiency is the term used to evaluate public health interventions using cost/benefit ratio analysis.

Practice Questions

Questions 12–15

Among 245 college students who dedicated 1 month of summer break to building homes for Habitat for Humanity, 12 developed back strains on the job. Based on the diagram of these 12 episodes of back strain, answer the following questions:



Response options for Questions 12–15:

A. 2/242	E. 3/245	I. 10/244
B. 2/244	F. 8/242	J. 10/245
C. 2/245	G. 8/244	K. 12/245
D. 3/242	H. 8/245	

12. What is the point prevalence on July 15, 12:01 am?
13. What is the point prevalence on July 31, 11:59 pm?
14. What is the incidence rate for the period July 15–July 31?
15. What is the period prevalence for July 15–July 31?

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12. **Answer: C**. On July 15, there were 2 students with symptoms of back strain (E, K).
13. **Answer: E**. On July 31, there were 3 students with symptoms of back strain (B, G, I).
14. **Answer: H**. Eight new cases of back strain had onset between July 15 and July 31 (A, B, D, F, G, I, J, L).
15. **Answer: J**. A total of 10 students had symptoms of back strain at some time from July 15–31, including 2 with onset prior to July 15 (E, K) and 8 with onset during the period July 15–31 (A, B, D, F, G, I, J, L).

VITAL STATISTICS AND RATES

Birth Rate

Birth rate (also called crude birth rate) is the rate of live births in a population during a time period (usually the calendar year).

$$\textbf{Simple formula:}\ \frac{\text{Live births}}{\text{Population}} \times 1{,}000$$

This can be interpreted as **births per 1,000 population**. The U.S. birth rate (in 2010) was 13.0 births/1,000 population.

Fertility Rate

Fertility rate is the rate of live births among women of childbearing age (age 15–49) in a population during a time period (usually the calendar year).

$$\textbf{Simple formula:}\ \frac{\text{Live births}}{\text{Women of childbearing age}} \times 1{,}000$$

This can be interpreted as **births per 1,000 women of child-bearing age**. The U.S. fertility rate (in 2010) was 64.1 births/1,000 women of child-bearing age.

Mortality Rate

Mortality rate (also called death rate or crude death rate) is the rate of deaths in a population during a time period (usually the calendar year).

$$\textbf{Simple formula:}\ \frac{\text{Deaths}}{\text{Population}} \times 1{,}000$$

This can be interpreted as **deaths per 1,000 population**. Mortality rate may be affected by the age structure in different populations, so be sure to account for age structure before comparing mortality rates in different countries. The U.S. mortality rate (in 2010) was 8.4 deaths/1,000 population.

Infant Mortality Rate

Infant mortality rate is the yearly rate of deaths among children age <1 in relation to the number of live births during the same year. Within a population, the infant mortality rate is a key indication of the population's health status.

$$\textbf{Simple formula:}\ \frac{\text{Infant deaths}}{\text{Live births}} \times 1{,}000$$

This can be interpreted as **infant deaths per 1,000 live births**. The U.S. infant mortality rate (in 2010) was 6.14 infant deaths/1,000 live births.

$$\textbf{Neonatal mortality rate:}\ \frac{\text{Infant deaths prior to day 28}}{\text{Live births}} \times 1{,}000$$

$$\textbf{Postneonatal mortality rate:}\ \frac{\text{Infant deaths from day 28–365}}{\text{Live births}} \times 1{,}000$$

Infant mortality rate: Neonatal mortality rate + Postneonatal mortality rate

Perinatal mortality rate: Stillbirths + $\frac{\text{Deaths in the first week of life}}{\text{Live births}} \times 1{,}000$

Infant Mortality

The top 3 causes of infant mortality are **birth defects** (24%), **low birth weight (<1,500 g)/respiratory distress** (18%), and **SIDS** (16%). SIDS rates can be reduced sharply if infants are prevented from sleeping on their stomachs.

Other facts about infant mortality:

- Native Americans have highest rates of SIDS.
- Blacks have highest rates of infant mortality due to low birth weight and infections; number 1 killer of black infants is low birth weight.
- Hispanic profile is similar to whites, but slightly higher.

Sociologic risk factors for children include:

- Maternal immaturity: risk of premature birth increases dramatically below age <19
- Poverty: major risk factor for prematurity and other unfavorable outcomes
- Single-parent family: correlated with child abuse, childhood suicide, truancy, and delinquency

Maternal Mortality Ratio

Maternal mortality ratio is the ratio of deaths in women from all causes associated with childbirth in relation to the number of live births during the same year. The denominator is **per live births**.

Simple formula: $\frac{\text{Maternal deaths}}{\text{Live births}} \times 100{,}000$

This can be interpreted as **maternal deaths per 100,000 live births**; this is an **important index** of maternal care. The U.S. maternal mortality ratio (in 2010) was 7.1 maternal deaths/100,000 live births.

Case Fatality Rate

Case fatality rate (CFR) is the percentage of cases of an illness or medical condition that result in death within a specified time period.

Simple formula: $\frac{\text{Deaths}}{\text{Cases}} \times 100$

This can be interpreted as **proportion of cases which end in death (fatality)**. For instance, in a population of 200 people, 25 become ill, and 5 die from the illness. Therefore, CFR is 5 deaths/25 cases × 100 = 20%.

Proportionate Mortality Rate

Proportionate mortality rate (PMR) is the percentage of deaths from all causes that are due to a specified cause during a specified time period.

$$\textbf{Simple formula:}\ \frac{\text{Deaths from a specified cause}}{\text{Total deaths}} \times 100$$

This can be interpreted as **proportion of deaths from a specific cause**. The PMR is used for the most common causes of death in a population.

Table II-20-2. Types of Measured Rates

Crude mortality rate	Deaths per population
Cause-specific mortality rate	Deaths from a specific cause per population
Case-fatality rate	Deaths from a specific cause per number of persons with the disease
Proportionate mortality rate (PMR)	Deaths from a specific cause per all deaths

Practice Questions

Response options for Questions 16–18:

A. Birth rate
B. Fertility rate
C. Infant mortality rate
D. Maternal mortality ratio
E. Age-adjusted rate
F. Case-fatality rate
G. Sex-adjusted rate
H. Proportionate mortality rate
I. Age-specific rate
J. Sex-specific rate
K. Age- and sex- and race/ethnicity-specific rate

16. Rate of live births among women of childbearing age
17. Proportion of cases of a disease that die from that disease
18. Rate of homicide in black men, age 15–24

16. **Answer: B**. Restatement of definition of fertility rate
17. **Answer: F**. Restatement of definition of case-fatality rate
18. **Answer: K**. Homicide rate restricted to black men in the age range 15–24

Practice Questions

Questions 19 and 20 are based on the following table

Incidence and Mortality of Disease

Age	Disease A		Disease B		Total	
Groups	Cases	Deaths	Cases	Deaths	Deaths	Population
0–12	2	1	300	1	40	22,000
13–24	101	34	267	0	30	18,000
25–64	50	42	1,042	2	125	50,000
>64	0	0	986	95	303	30,000
Totals	153	77	2,595	98	498	120,000

19. The case-fatality rate for Disease A is

    A. 77/120,000 × 1,000
    B. 77/120,000 × 100,000
    C. 153/120,000 × 100,000
    D. 153/498 × 100
    E. 77/153 × 100

20. The proportionate mortality rate for Disease B is

    A. 98/120,000 × 100,000
    B. 2,595/120,000 × 100,000
    C. 98/2,595 × 100
    D. 98/498 × 100
    E. Cannot be determined

19. **Answer E**. For CFR, denominator is total cases of disease A.

20. **Answer D**. For proportionate mortality, denominator is total deaths.

YEARS OF POTENTIAL LIFE LOST AND SURVIVAL ANALYSIS

YPLL is an indicator of premature death. The YPLL for a particular cause of death is the sum, over all persons dying from the cause, of the years that those persons would have lived had they experienced normal life expectancy.

Assume life expectancy is 75 years. A person who dies at age 65 would be dying 10 years prematurely (75 − 65 = 10 YPLL). For 100 such people, the YPLL calculation would be 100 × (75 2 65) = 1,000 YPLL.

In the United States, the leading cause of YPLL age 65 is unintentional injury.

Survival Analysis

Survival analysis is a class of statistical procedures for estimating the proportion of people who survive in relation to the length of survival time. The starting point is 100% survival. In 2000, the median survival time was age 78.

A survival curve is a curve that starts with 100% of the study population and shows the percentage of the population still surviving at successive times for as long as information is available.

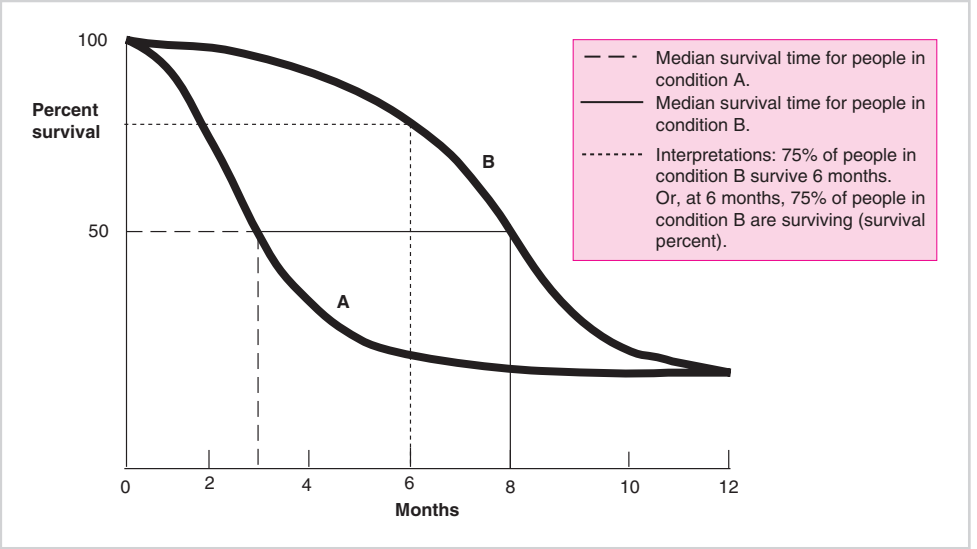


Figure II-20-5. Survival Curve

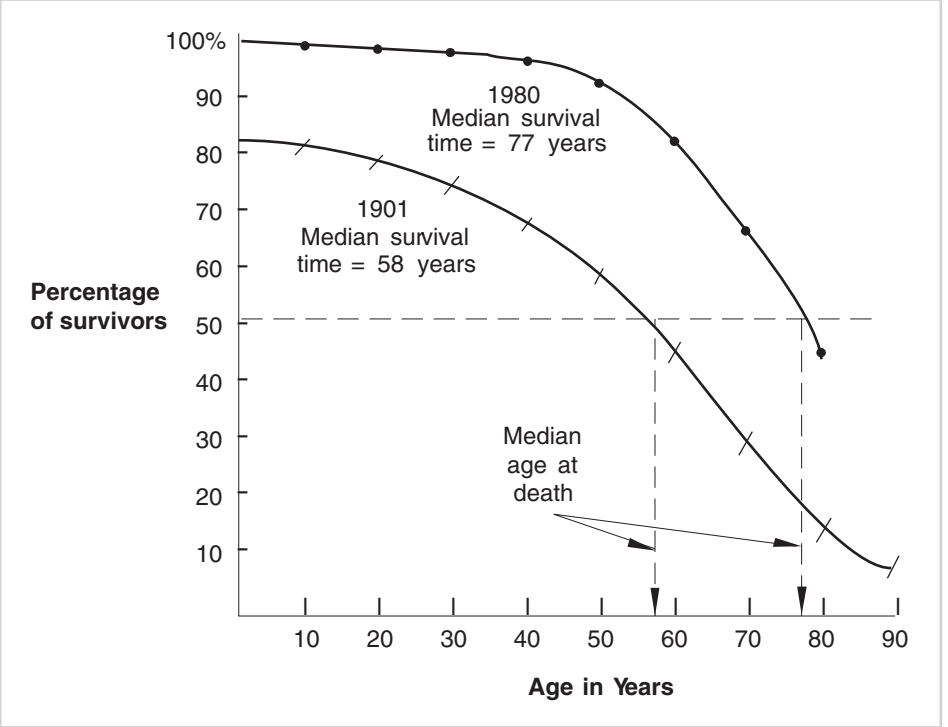


Figure II-20-6. Percentage of Survivors at Specified Ages, 1901 and 1980

SCREENING TESTS

Screening is the process of using tests to permit early detection of risk factors, asymptomatic infection, or early stages of clinical disease, thus permitting early diagnosis and early intervention/treatment. Screening is usually applied to populations of apparently healthy individuals. Illness, if present, is asymptomatic (subclinical, inapparent).

- Screening tests allow for earlier detection and earlier diagnosis. Hopefully, earlier treatment will effect a more favorable clinical course. Good screening tests usually require **high sensitivity** (low false-negative rate, almost everyone who has disease tests positive), because the consequences of missing a positive disease state may be severe. Therefore you can **rule a disease out** if a screening test is negative. Positive screening tests can be followed up with confirmatory tests.

  Confirmatory tests are performed after a screening test results positive. The goal is to be certain that the individual has the disease, which means that a **high specificity** is desired (low false-positive rate, almost everyone who does not have the disease would test negative). Therefore a **disease can be ruled in** if a confirmatory test is positive.
- Screening test results are classified as **positive** (presumed by the test to be diseased) or **negative** (presumed by the test to be healthy).

Classic 2 × 2 Table

The 2 × 2 table is the standard form for displaying screening test results in relation to disease status. Disease status categories (diseased and healthy) are diagrammed in the vertical columns. Screening test results (positive, negative) are diagrammed in the horizontal dimension.

Table II-20-3. Classic 2 × 2 Table

	Disease	No Disease	Totals
Positive	True Positive [TP]	False Positive [FP]	TP + FP
Negative	False Negative [FN]	True Negative [TN]	TN + FN
Totals	TP + FN	TN + FP	TP + TN + FP + FN

In the 2 × 2 table, **positive (P) and negative (N) refer to the actual screening test results**, while **true (T) and false (F) refer to the agreement of screening test results with the gold standard**.

- **True Positives:** diseased people correctly classified as positive
- **True Negatives:** healthy people correctly classified as negative
- **False Positives:** healthy people misclassified as positive
- **False Negatives:** diseased people misclassified as negative

Table II-20-4. Screening Results in a 2 × 2 Table

		Disease				
		Present		Absent		Totals
Screening Test Results	Positive	TP	80	FP	40	TP + FP = 120
	Negative	FN	20	TN	60	TN + FN = 80
	Totals	TP + FN = 100		TN + FP = 100		TP + TN + FP + FN = 200

Note

On the exam, do not rely on a certain orientation of the table to locate TP, TN, FP, or FN. Tables may be presented in any orientation.

Familiarize yourself with the data and remember how these concepts are defined.

Measures of Screening Test Performance

Sensitivity is the number of people with the disease who test positive divided by the total number of people with the disease. In other words, "Out of all the people who have the disease, how many tested positive?"

Highly sensitive tests identify most, if not all, cases of the disease. Sensitivity is particularly important to have when the consequences of missing a disease are severe, e.g., missing an early detection of cancer before it progresses to an advanced stage.

- Sensitivity = TP/All people with disease
- Sensitivity = **TP/(TP + FN)** (in the example above, 80/80 + 20 = 80/100 or 80%)

Specificity is the number of people without the disease who test negative divided by the total number of people without the disease. In other words, "Out of all the people who do not have the disease, how many tested negative?"

Highly specific tests are used to confirm a diagnosis ("rule in") because there are very few FP results.

- Specificity = TN/All healthy people
- Specificity = **TN/(TN + FP)** (in the example above, 20/20 + 80 = 20/100 or 20%)

Sensitivity and specificity are fixed characteristics of the screening test. They will change as you vary the cutoff point, but they are not changed or affected by the prevalence of disease. Sensitivity and specificity are 2 elements of test validity.

Predictive value represents the percentage of test results that match the diagnosis of the patient. It is affected by the disease prevalence in the given population.

- **Positive predictive value (PPV)** is the proportion of people with a positive screening test result who are diseased (i.e., that a person with a positive test is a true positive). **Increased specificity means increased PPV, because FP will be fewer. As prevalence increases, PPV will increase.**
  - PPV = TP/All people with a positive test result
  - PPV = TP/(TP + FP)
- **Negative predictive value (NPV)** is the proportion of people with a negative screening test result who are well (i.e., that a person with a negative test is a true negative). In a 2 × 2 table, NPV is located on the bottom row. **Increased sensitivity means increase NPV, because FN will be fewer. As prevalence decreases, NPV will increase.**
  - NPV = TN/All people with a negative test result
  - NPV = TN/(TN + FN)

Increased prevalence of a disease **will increase PPV and decreased NPV**. Decreased prevalence of a disease **will decrease PPV and increase NPV.**

- Prevalence = (TP + FN)/(TP + TN + FN + FP)

Likelihood ratio is the expression of how much more (or less) likely a test result is to be found in nondiseased (or diseased) compared with diseased (or nondiseased).

- Positive likelihood ratio (LR+) is the proportion of diseased people to that of nondiseased people with a positive test result.

$$\text{LR+} = \frac{\text{Sensitivity}}{1 - \text{Specificity}} \text{ OR } \frac{\text{Sensitivity}}{\text{FP}/(\text{TN} + \text{FP})} \text{ OR } \frac{\text{Sensitivity}}{\text{FP rate}}$$

- Negative likelihood ratio (LR−) is the proportion of diseased people to that of non-diseased people with a negative test result.

$$LR- = \frac{1 - \text{Sensitivity}}{\text{Specificity}} \text{ OR } \frac{FN/(TP + FN)}{\text{Specificity}} \text{ OR } \frac{\text{FN rate}}{\text{Specificity}}$$

Screening Test Diagram

The screening test diagram displays the distributions of the screening test measure separately for people with disease and people with no disease. The cutoff point (threshold) divides screened people into test-positive and test-negative categories.

- People with no disease are either correctly classified as TN or misclassified as FP.
- People with disease are either correctly classified as TP or misclassified as FN.

The screening test diagram is a useful model of the real world in which values of screening test measures (such as blood glucose) are generally different for diseased (diabetic) and nondiseased (non-diabetic) people, but the distributions overlap. For example, a random blood glucose >200 may be considered the cutoff point to diagnose diabetes. However, a few individuals who are non-diabetic may have a random blood glucose >200, and some diabetics will have a random blood glucose <200.

The measures of screening test performance can be displayed on the screening test diagram by identifying the appropriate areas under the curves. For example, the numerator for sensitivity is TP, whereas the denominator is everyone under the curve labeled "disease."

Sensitivity and specificity are fixed characteristics of the screening test; they are both elements of **test validity**.

Note that changing the cutoff point changes the sensitivity and specificity of the test.

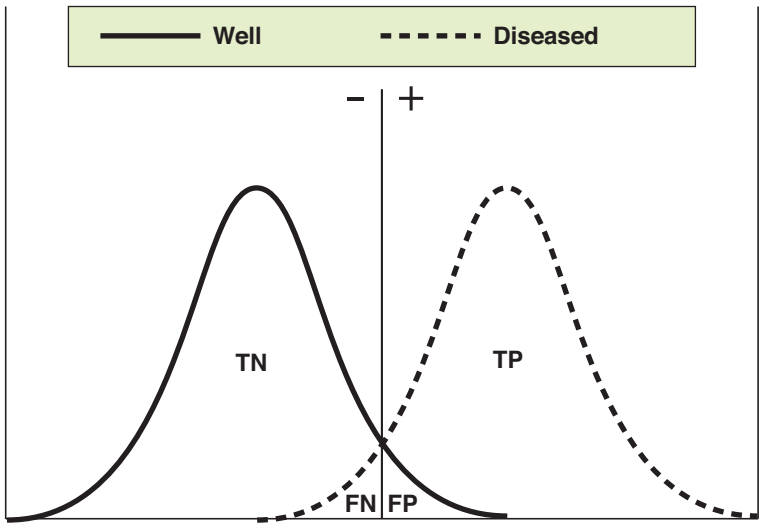


Figure II-20-7. Screening Test Diagram

This is a graphical representation of sensitivity and specificity in a screening test. The area under the curve for the false-negative rate is very low, which implies very high sensitivity. Likewise, the area under the curve for the false-positive rate is low, implying a high specificity.

Reliability indicates the degree of reproducibility (consistency) of screening tests. In other words, does the test yield the same results when performed under the same circumstances by the same personnel? Reliability is sometimes referred as **precision.**

Validity indicates the degree in which a test distinguishes healthy from diseased individuals. Sensitivity and specificity are both elements of validity. Validity is sometimes referred as **accuracy**.

Receiver operating characteristic (ROC) curves are a way of depicting and comparing the sensitivity and specificity of different clinical tests used for the same disease. Sensitivity is plotted on the *y*-axis and 1-specificity is plotted on the *x*-axis. The "curve" for a given test is produced as the cutoff point is varied, showing the range of sensitivity and specificity you would get at various cutoff points.

Ideal tests approach 100% sensitivity and specificity, which would produce a curve very close to the left upper corner of the ROC plot. In general, the farther to the upper left corner that a curve reaches, the better (more valid) a test will be.

Sometimes data is collected by human "observers" with some degree of subjectivity, e.g., radiologists may not always agree on x-ray interpretations, and pathologists may not always agree on a histologic diagnosis. In these cases it is beneficial to characterize how much agreement or variation exists between different observers, using the **kappa statistic** (κ). Kappa statistic is defined as the **degree of agreement between 2 observers**. The maximum value is 1.0, which would represent perfect agreement. Generally, $\kappa < 0.40$ represents poor agreement, κ 0.40-0.75 represents moderate agreement, and $\kappa > 0.75$ represents excellent agreement.

Practice Questions

A new screening test is applied to a representative sample of 1,000 people in the population. Based on the data presented in the following table, calculate the requested screening test measures.

	Diseased	Healthy	
Positive	90	60	150
Negative	10	840	850
	100	900	1,000

Response options for Questions 21–27:

A. 90/150	G. 840/850	M. 60/900
B. 90/100	H. 840/900	N. 60/150
C. 90/1,000	I. 930/1,000	O. 10/100
D. 90	J. 900/1,000	P. 10/850
E. 60	K. 100/1,000	
F. 10	L. Cannot be calculated	

21. What is the sensitivity of the screening test?
22. What is the specificity of the screening test?
23. What is the positive predictive value of the screening test?
24. What is the number of false negative tests?
25. What is the number of false positive test results?
26. What is the prevalence of disease, assuming screening of a representative sample?
27. What is the false positive rate?

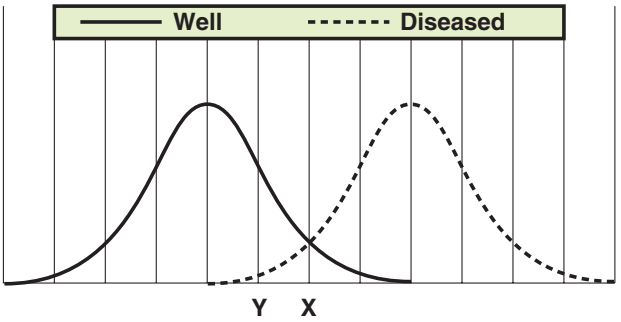
---

21. **Answer: B**. Sensitivity = TP/All diseased people = 90/100
22. **Answer: H**. Specificity = TN/All healthy people = 840/900
23. **Answer: A**. PPV = TP/All test positives = 90/150
24. **Answer: F**. Diseased people misclassified by the test = 10
25. **Answer: E**. False positives = Healthy people who are misclassified by the test = 60
26. **Answer: K**. Prevalence = All diseased people/All screened people = 100/1,000
27. **Answer: M**. False positive rate = FP/All healthy people = 60/900

Practice Questions

Questions 28–33

The CDC is concerned about optimizing the detection of a disease that poses a serious public health threat. CDC health officials are considering lowering the usual screening test cutoff point from X to Y.



28. Moving cutoff in the manner being considered by the CDC causes the number of false positives to
    A. increase
    B. decrease
    C. remain unchanged
    D. cannot be determined

29. Moving the cutoff in the manner being considered by the CDC causes the positive predictive value to
    A. increase
    B. decrease
    C. remain unchanged
    D. cannot be determined

30. Moving the cutoff in the manner being considered by the CDC causes the accuracy to
    A. increase
    B. decrease
    C. remain unchanged
    D. cannot be determined

31. Moving the cutoff in the manner being considered by the CDC causes the sensitivity to
    A. increase
    B. decrease
    C. remain unchanged
    D. cannot be determined

(*Continued*)

Practice Questions (*continued*)

32. Assuming that everyone who receives a positive test result is referred for medical follow-up, moving the cutoff in the manner being considered by the CDC will cause the numbers of screened people who are referred for follow-up to

    A. increase
    B. decrease
    C. remain unchanged
    D. Cannot be determined

33. At Cutoff Point X, sensitivity is

    A. 100%
    B. 85%
    C. 50%
    D. 25%
    E. 0%

28. **Answer: A**. At Y, FP will increase as more well people are misclassified.

29. **Answer: B**. Although there will be more TP at Cutoff Y, there will be a large increase in numbers of FP. The ratio, TP/(TP + FP), will decrease. A positive test result will be less predictive of actual disease.

30. **Answer: B**. X is the point of overlap and the point of maximal accuracy. Moving to Y will decrease accuracy.

31. **Answer: A**. At Y, more diseased people will receive a (correct) positive test result. They will be TP. TP, the numerator for sensitivity, will increase while the denominator (total people with disease) will be unchanged.

32. **Answer: A**. Larger numbers of people would be screened positive at Cutoff Y and referred for follow-up.

33. **Answer: B**. Notice that Cutoff Point X separates the curve of diseased people into 2 areas; above the cutoff point, approximately 85% of diseased people receive a (correct) positive test result. They are true positives. Sensitivity = TP/All people with disease.

Practice Questions

34. A physician interviews an 18-year-old woman who says she has just received a negative syphilis test result from the county health department. She describes her sense of relief. She discloses that she is a sex worker who "works the street" 4–5 nights a week. She has been doing this for the past 18 months. Typically, she has oral or vaginal sex with 5–8 customers per night. For a higher fee she will have sex without requiring her customer to wear a condom. On the basis of these findings, the physician is likely to be most concerning with which of the following screening test measures?

    A. Sensitivity
    B. Specificity
    C. Positive predictive value
    D. Negative predictive value
    E. Accuracy

35. A 55-year-old man visits his primary care physician with a complaint of urinary infrequency. Examination finds a 1-cm nodule on his prostate gland. The physician orders a prostate-specific antigen (PSA) serum test. By common standards, a PSA level >4 ng/mL is considered abnormal. Using this standard, this test has a sensitivity of 80% and a specificity of 90%. A recently published epidemiologic article found that in a cross-sectional study, 10% of men of this age have prostate cancer. The patient's PSA is tested to be 7 ng/mL. What is your best estimate of the likelihood that this man actually has prostate cancer?

    A. 2
    B. 53
    C. 98
    D. 47%
    E. Insufficient information

34. **Answer: D**. Disease prevalence affects the predictive value of the test. The greater the prevalence, the higher the PPV of the test. Screening tests are generally performed in high-risk populations (where the PPV is greater). NPV is the proportion of individuals who test negative who are actually free from disease. When the prevalence of disease is high, the negative predictive value will be low. As a result, her negative results are concerning because she is part of a high prevalence group, and the predictive value of her negative test is low.

35. **Answer: D**. Here, you have to recreate a 2x2 table. You are provided a disease prevalence of 10%. This information can be used to create the lower border of the table using hypothetical numbers. You are also given a sensitivity of 80%, therefore 80% of 10 = 8 for upper right quadrant cell. For the given specificity of 90%, 90% of 90 = 81. Then, fill in the blank fields by deduction.

		Disease Present	Disease Absent		Equation
Test Result	Positive	8	9	17	$PPV = \frac{8}{8+9} = \frac{8}{17} = 47\%$
	Negative	2	81	83	$NPV = \frac{81}{81+2} = \frac{81}{83} = 98\%$
	Equation	10	90	100	

STUDY DESIGNS

When epidemiologists observe the relationship between exposures and disease outcomes in free-living populations, they are conducting **observational studies**. When epidemiologists or clinicians test interventions aimed at minimizing the disease-producing exposures and optimizing health-promoting exposures or factors, they are performing **experimental studies**.

- In observational studies, nature is allowed to take its course; no intervention; not randomized
- In experimental studies, there is an intervention and the results of the study assess the effects of the intervention

Observational Studies

A **case report** is a brief, objective report of a clinical characteristic or outcome from a single clinical subject or event, n = 1; for example, a 23-year-old man with treatment-resistant TB. No control group. A **case series report** is an objective report of a clinical characteristic or outcome from a group of clinical subjects, n >1, i.e., patients at local hospital with treatment-resistant TB. No control group.

In a **cross-sectional study**, the **presence or absence of disease** (and other variables) is determined in each member of the study population or in a representative sample at a particular time. The co-occurrence of a variable and the disease can be examined.

- Disease prevalence rather than incidence is recorded.
- The temporal sequence of cause and effect cannot usually be determined in a cross-sectional study, e.g., who in the community now has treatment-resistant TB.

A **case-control study** identifies a **group of people with the disease and compares them with a suitable comparison group without the disease.** It is almost always retrospective, e.g., comparing cases of treatment-resistant TB with cases of nonresistant TB. A case-control study is very useful for **studying conditions with very low incidence or prevalence.**

- Cannot assess incidence or prevalence of disease
- Can help determine causal relationships

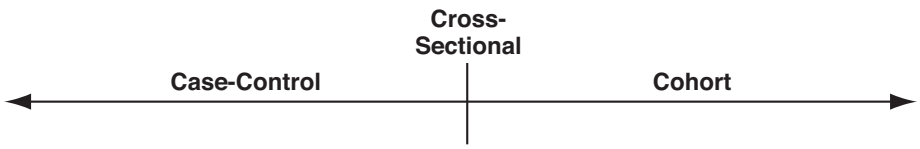


Figure II-20-8. Differentiating Study Types by Time

In a **cohort study**, a population group who has been exposed to the risk factor is identified and followed over time and compared with a group not exposed to the risk factor. Outcome

is disease incidence in each group, e.g., following a prison inmate population and marking the development of treatment-resistant TB. Cohort studies are **used for more common diseases**.

- Allows you to evaluate whether potential risk factors are related to subsequent outcomes
- Prospective subjects tracked forward in time (may occasionally be retrospective; risk factor exposure/nonexposure is followed over time past-present)
- Can determine incidence and causal relationships
- Must follow population long enough for incidence to appear
- Historical examples: Framingham study, a long-term study started in 1948, now in the third generation

Analyzing observational studies

For cohort studies, use relative risk and/or attributable risk to measure effect.

Relative risk (RR): Comparative probability asking how much more likely the exposed person is going to get the disease compared to the non-exposed.

- Incidence rate of exposed group **divided by** the incidence rate of the unexposed group. How much greater chance does one group have of contracting the disease compared with the other group?
- For example, if infant mortality rate in whites is 8.9 per 1,000 live births and 18.0 in blacks per 1,000 live births, then the RR of blacks versus whites is 18.0 divided by 8.9 = 2.02. Compared with whites, black infants are 2× as likely to die in the first year of life. **Infant mortality is not a true rate**. The calculation for RR remains unaffected in this calculation.

Attributable risk (AR) (also called absolute risk reduction): Comparative probability asking how many more cases in one group.

- Incidence rate of exposed group minus the incidence rate of the unexposed group
- Using the same example, attributable risk is equal to 18.0 – 8.9 = 9.1. Of every 1,000 black infants, there were 9.1 more deaths than were observed in 1,000 white infants. In this case, attributable risk gives the excess mortality.
- Note that both RR and AR tell us if there are differences but do not tell us why those differences exist.

$$\textbf{AR percentage} = \frac{\text{Incidence in exposed} - \text{Incidence in unexposed}}{\text{Incidence in exposed, e.g., } \frac{18 - 8.9}{18} = 51\% \text{ attributable risk percentage}}$$

This implies that 51% of the excess infant mortality is seen in black infants.

For case-control studies, use odds ratio.

Odds ratio (OR) (also called relative odds) looks at the increased odds of getting a disease with exposure to a risk factor versus non-exposure to that factor. OR can be calculated from a cohort or case control study.

- Odds of exposure for cases divided by odds of exposure for controls
- Odds that a person with lung cancer was a smoker versus the odds that a person without lung cancer was a smoker

Table II-20-5. Odds Ratio

	Lung Cancer	No Lung Cancer
Smokers	659 (A)	984 (B)
Nonsmokers	25 (C)	348 (D)

$$OR = \frac{A/C}{B/D} = \frac{AD}{BC}$$

Use OR = AD/BC as the working formula. For the above example:

$$OR = \frac{AD}{BC} = \frac{659 \times 348}{984 \times 25} = 9.32$$

The odds of having been a smoker are more than 9× greater for someone with lung cancer compared with someone without lung cancer.

The interpretation of OR is as follows:

- **OR <1:** exposure negatively associated with disease
- **OR = 1:** exposure not related to disease
- **OR >1:** exposure more related to disease

Note

Probability is the likelihood of an event occurring, e.g., the probability of rain today is 75%. **Odds ratio** (or relative odds) looks at the probability the event occurs divided by the probability it will not occur:

0.75/1-0.75 = 0.75/0.25 = 3 to 1 relative odds

Practice Questions

36. How would you analyze the data from this case-control study?

	No Colorectal Cancer	Colorectal Cancer	TOTALS
Family history of colorectal cancer	120	60	180
No family history of colorectal cancer	200	20	220
TOTALS	320	80	400

36. **Answer:** The odds of having colorectal cancer are 5x greater for those who have a family history.

$$OR = \frac{AD}{BC} = \frac{(60)\ (200)}{(120)\ (20)} = 5.0$$

Table II-20-6. Differentiating Observational Studies

Characteristic	Cross-Sectional Study (Prevalence Study)	Case-Control Study	Cohort Study
Time	One time point	Retrospective	Prospective (sometimes retrospective)
Incidence	No	No	Yes
Prevalence	Yes	No	No
Causality	No	Yes	Yes
Role of disease	Measure disease	Begin with disease	End with disease
Assesses	Simultaneous assessment of risk factor and disease assess disease burden	Many risk factors for single disease	Single risk factor affecting many diseases
Data analysis	Chi-square to assess association	Odds ratio to estimate association	May calculate relative risk or attributable risk

Table II-20-7. Computational Measures by Type of Observational Study

Measure	Cross-Sectional Study Prevalence Study	Case-Control Study	Cohort Study
Prevalence of disease	Yes	No	No
Prevalence of exposure	Yes	No	No
Odds ratio	No	Yes	Yes
Incidence rate in the exposed	No	No*	Yes
Incidence rate in the nonexposed	No	No*	Yes
Relative risk	No	No	Yes
Attributable risk	No	No	Yes

*In a case control study, calculate the *proportion* (not incidence) of patients with disease who were exposed.

Experimental Studies: Clinical Trials

Clinical trials (intervention studies) use research which involves the administration of a test regimen to evaluate its safety and efficacy. In clinical trials, subjects who do not receive the intervention under study are called the **control group**. The goal is to have a source of comparison to ensure the experiment group is being affected by the intervention and not by other factors (most often a placebo group). To reduce confounding, control group subjects must be as similar as possible to intervention group subjects.

To obtain approval from the FDA, 3 phases of clinical trials must be passed:

Phase 1: testing safety in healthy volunteers

Phase 2: testing protocol and dose levels in small group of patient volunteers

Phase 3: (considered the definitive test): testing efficacy and occurrence of side effects in larger group of patient volunteers

In a **randomized controlled clinical trial** (RCT), subjects are randomly allocated into "intervention" and "control" groups to receive (or not) receive an experimental procedure or intervention. RCTs are generally regarded as the **most scientifically rigorous** studies available in epidemiology.

Double-blind RCT is the type of study least subject to bias, but also the most expensive to conduct. Double-blind means that neither subjects nor researchers who have contact with them know whether the subjects are in the treatment or comparison group.

Community trials are experiments in which the unit of allocation to receive a preventive or therapeutic regimen is an entire community or geographical area, such as a city, village, or school. Does the treatment work in real world circumstances? This type of study is also important when it is impossible to randomize or assign just one individual to treatment or control because the intervention "bleeds" or affects everyone around them. For example, if you wanted to assess whether a physician having access to an online database will help to improve evidence-based care, you cannot randomize physicians working in the same hospital because they will likely share the resource and information. Instead, you must randomize different entire hospitals to either receive access to the database or not.

Crossover studies are studies in which each group functions as the intervention and the control, but at different times. This is best utilized for a condition that has chronic symptoms that respond immediately to a therapy, and with an intervention that is short-acting. A common example is asthma. Suppose a new inhaler is tested on 40 individuals with severe persistent asthma: 20 receive the new inhaler and 20 receive a placebo for 1 week and symptoms are monitored. The medications are then stopped for 2 days ("wash-out" period). The groups then switch and receive the new inhaler/placebo for 1 more week.

Table II-20-8. Comparison of Case-Control and Cohort Studies

Case-Control Study	Cohort Study
Small number of subjects	Large number of subjects
Lower cost	Higher cost
Short time period	Longer time period
One disease: multiple past exposures	**One exposure: multiple future diseases**
Low prevalence or high prevalence diseases	High incidence diseases only
Potential for recall bias	Potential for selection bias

STUDY DESIGNS: BIAS IN RESEARCH

Bias versus Confounding

A **bias** is defined as any systematic error in a study which causes an inaccuracy in the estimation of association between risk factor (exposure) and disease. This can be caused by a problem in the design, execution, data collection, or data analysis.

Confounders (confounding variables) are variables that may cause a bias in a study (**confounding bias**). In the simplest definition, a confounder is a variable associated with the exposure and outcome of interest that causes us to mistake our assessment of the relationship between the exposure and outcome of interest.

- We are interested in assessing the effect of exposure A on disease X, and observe that A is associated with X.
- Exposure B is a known risk factor for disease X.
- B and A are associated with each other but do not cause each other.
- Therefore, A is associated with B, and B causes X, so it falsely appears to us that A causes X.

For example, we observe that coffee drinkers have a higher risk for lung cancer than non-coffee drinkers, and interpret that coffee might contribute to causing lung cancer. However, people who drink coffee also tend to smoke cigarettes, and we may see that there is a much higher rate of smoking in the coffee drinking group than in the non-coffee drinking group. Cigarette smoking is a known risk factor for lung cancer, and because there are far more smokers in the coffee drinking group, this causes confounding in our observation of the association between drinking coffee and developing lung cancer.

Confounders may be "known" or "unknown." If the confounders are known, we can account for them by making sure our intervention and control groups are matched with respect to the confounder, prior to beginning the study (e.g., equal proportions of age, sex, smoking status). We can also account for known confounders in data analysis by stratification/adjustment; that is, comparing outcomes in equivalent groups. Multivariable linear or logistic regression models allow us to adjust for several variables simultaneously.

The problem is that there will almost always be unknown confounders: we don't know what they are and therefore we can't adjust for them. This is minimized by randomization, because we assume that the randomization process will evenly distribute all known and unknown confounding variables between the intervention and control groups. Therefore the confounding variables will not be overrepresented in one group, and we will be able to observe the effect of the exposure on the outcome.

There are ways to handle confounding in studies.

Prior to beginning the study:

- Match the control and intervention groups with respect to confounding variables that we know about (sex, smoking status, family history of diabetes, etc.)
- Randomize patients to control or intervention groups, so that any confounders are likely to be evenly distributed between groups, and we won't need to worry about any known or unknown confounders

When analyzing data after the study is complete:

- Analyze stratified or adjusted data; that is, split the groups up according to the known confounding variables and only compare outcomes within the same strata (e.g., compare outcomes between elderly people and compare outcomes between young people)

Types of Bias

Selection bias (sampling bias): the sample selected is **not representative of the population**. For example:

- Predicting rates of heart disease by gathering subjects from a local health club
- Using only hospital records to estimate population prevalence (Berkson's bias)
- People included in study are different from those who are not (nonrespondent bias)

Measurement bias (or information bias): information is gathered in a manner that distorts the information. For example:

- Measuring patients' satisfaction with their respective physicians by using leading questions, such as, "You don't like your doctor, do you?"
- Subjects' behavior is altered because they are being studied (Hawthorne effect). This is a factor only when there is no control group in a prospective study.

Experimenter expectancy (Pygmalion effect): experimenter's expectations are inadvertently communicated to subjects, who then produce the desired effects. Can be avoided by **double-blind design**, where neither the subject nor the investigators know which group receives the intervention under study and which group is the control.

Lead-time bias: gives a false estimate of survival rates. For example, patients seem to live longer with the disease after it is uncovered by a screening test. Actually, there is no increased survival, but because the disease is discovered sooner, patients who are diagnosed seem to live longer.

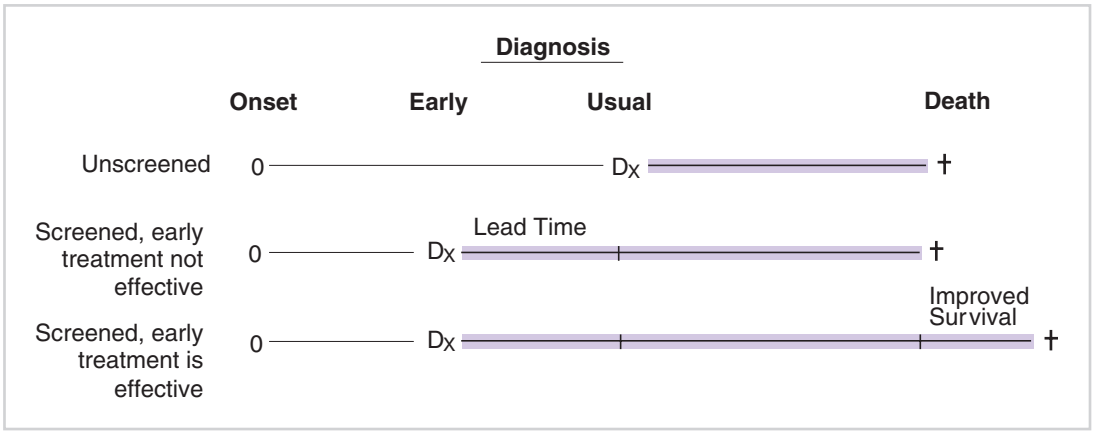


Figure II-20-9. Diagnosis, Time, and Survival

Recall bias: subjects fail to accurately recall events in the past. For example, how many times last year did you kiss your mother? This is a likely problem in retrospective studies.

Late-look bias: individuals with severe disease are less likely to be uncovered in a survey because they die first. For example, a recent survey found that persons with AIDS reported only mild symptoms.

Table II-20-9. Type of Bias in Research and Important Associations

Type of Bias	Definition	Important Associations	Solutions
Selection	Sample not representative	Berkson's bias, nonrespondent bias	Random, independent sample
Measurement	Gathering the information distorts it	Hawthorne effect	Control group/placebo group
Experimenter expectancy	Researcher's beliefs affect outcome	Pygmalion effect	Double-blind design
Lead-time	Early detection confused with increased survival	Benefits of screening	Measure "back-end" survival
Recall	Subjects cannot remember accurately	Retrospective studies	Confirm information with other sources
Late-look	Severely diseased individuals are not uncovered	Early mortality	Stratify by severity

Practice Questions

Response options for Questions 37–41:

A. 520/695
B. 600/1,000
C. 520/600
D. 695/1,000
E. 80/305
F. (520/695)/(80/305)
G. (520 × 225)/(175 × 80)
H. (520/695) – (80/305)
I. Cannot be determined for this type of study

	Disease	Well	
Exposed	520	175	695
Nonexposed	80	225	305
	600	400	1,000

37. Assume the table represents a cross-sectional study: What is the relative risk?
38. Assume the table represents a case-control study: What is the odds ratio?
39. Assume the table represents a cross-sectional study: What is the prevalence of disease?
40. Assume the table represents a disease outbreak investigation: What is the attack rate for people who did not eat the food?

(*Continued*)

Practice Questions (*continued*)

41. A study compares the effectiveness of a new medication for treatment of latent TB infection with the standard medication, isoniazid. Subjects with latent TB infection are sorted with equal likelihood of selection to receive the new medication or isoniazid. Neither the subjects themselves nor the clinicians know the treatment condition for each patient. This study is best described as a

    A. double-blind randomized cohort study
    B. randomized controlled trial with crossover design
    C. double-blind randomized clinical trial
    D. double-blind randomized clinical trial with crossover design
    E. double-blind quasi-experimental trial

37. **Answer: I**. Cannot calculate relative risk from a cross sectional study. Relative risk is calculated from a cohort study.

38. **Answer: G**. Odds ratio = A×D/B×C = 520×225/175×80

39. **Answer: B.** Add exposed and non-exposed with disease for numerator; denominator is population at risk = 600/1,000.

40. **Answer: E.** Attack rate for those who did not eat the food = number of people who did not eat the food who became ill over the total number at risk = 80/305

41. **Answer C:** This is the classic description of a double-blinded randomized clinical trial. "sorted with equal likelihood of selection" = randomized

Practice Questions

42. A group of 200 hypertensive subjects and a comparable group of 200 normotensive subjects are recruited and enrolled into a longitudinal study to examine the effect of a diagnosis of hypertension on subsequent occurrence of coronary heart disease. Study subjects are followed for 5 years. Final data are presented below. What is the attributable risk for hypertension? Indicate answer per 1,000.

	CHD	No CHD	Total
Hypertension	25	175	200
No hypertension	10	190	200
Total	35	365	400

    A. 75/100
    B. 250/1,000
    C. 35/1,000
    D. 125/1,000
    E. Cannot be computed for this type of study

(*Continued*)

Practice Questions (*continued*)

43. A study is conducted relating percentage of calories from fat in the habitual diet to subsequent incidence of clinical diabetes mellitus. Four groups of initially well persons are selected from the community to represent persons within each of 4 categories of fat intake. The percentages of daily calories from fat are: <20%, 20.40%, 35.49%, >50%. The groups are followed longitudinally for 5 years and assessed annually for diabetes. The type of study design is best described as a

    A. case-series trial
    B. case-control study
    C. cross-sectional study
    D. cohort study
    E. community trial

44. Alcohol consumption and cigarette smoking both contribute causally to the occurrence of esophageal cancer. These risk factors are not independent; in fact, they operate synergistically. A study of cigarette smoking in relation to esophageal cancer that fails to stratify or otherwise control for level of alcohol consumption would be guilty of which of the following threats to validity?

    A. Ascertainment bias
    B. Confounding
    C. Design bias
    D. Lead time bias
    E. Observer bias
    F. Recall bias
    G. Response bias
    H. Selection bias

42. **Answer: A.**

43. **Answer: D.**

44. **Answer: B.**

Biostatistics 21

Learning Objectives

- ❑ List the basic principles of probability and describe the connection to statistics
- ❑ Demonstrate how to calculate mode, mean, median, standard error, and standard deviation, and describe how they differ
- ❑ Describe the purpose of inferential statistical tests, such as student T test, chi-square, and analysis of variance
- ❑ Select an appropriate statistical test for a set of data to be analyzed

PROBABILITY

Independent events: the occurrence of one event does not affect the occurrence of another. For instance, the chance of a child being born with brown eyes is 0.75, and the chance of a child being born with blue eyes is 0.25. The eye color of the first-born child does not affect the eye color of the second-born.

- Calculate the probability of multiple independent events occurring by multiplying each individual probability together.
- For instance, the probability of having one child with brown eyes and one child with blue eyes is $0.75 \times 0.25 = 0.1875$ (18.75%).

Nonindependent events: the occurrence of one event affects the occurrence of another. For instance, a box has 5 white and 5 black balls inside. When picking the first ball, the probability of white is 0.5 and black is 0.5. If the first ball is black, the probability of the second ball being white is $5/9 = 0.56$ and black is $4/9 = 0.44$.

- Calculate the probability of multiple nonindependent events by multiplying each new probability, given that each previous event has occurred.
- For instance, the probability of choosing 2 black balls in a row followed by a white ball is $5/10 \times 4/9 \times 5/8$.

Mutually exclusive events: the occurrence of one event precludes the occurrence of another, i.e., both cannot happen. For instance, if a coin flip lands heads, it cannot land tails.

- Determine the combined probability of mutually exclusive events by addition.
- For instance, the probability of a coin flip landing heads or tails is $0.5 + 0.5 = 1.0$ (100%).

Non-mutually exclusive events: determine the combined probability (chance of either occurring) of two events by adding the two individual probabilities together and subtracting their product. If the chance of having diabetes is 10%, and the chance of someone being obese is 30%, the chance of meeting someone who is obese or had diabetes is $0.1 + 0.30 - (0.1 \times 0.30) = 0.37$ (or 37%).

Practice Questions

Survival Rates After Surgery

N	1 Year	2 Year	3 Year	4 Year
183	90%	75%	50%	40%

1. What is the average life expectancy after surgery?
2. If a patient survives for 2 years, what is the chance of surviving for 3 years?
3. In an effort to evaluate healthy lifestyle influences at home, a study is conducted to see how many pediatric patients have parents who exercise regularly. Parents at pediatric offices are questioned and it is concluded that 40% of pediatric patients have parents who exercise regularly. Assuming the events are independent, what is the probability that 2 pediatric patients with parents who exercise regularly will come into the office on the same day?

   (A) 0.16
   (B) 0.4
   (C) 0.8
   (D) 0.96
   (E) 0.08
   (F) 0.04

1. 3 years
2. 50/75
3. **Answer: A.** This requires the multiplication rule.

DESCRIPTIVE STATISTICS

Measures of Center

Measures of center identify a value in the middle of a distribution (data set), around which the rest of the data are centered.

Mean (or average) is the sum of the values of the observations divided by the number of observations.

$$\textbf{Mean} = \frac{\text{Sum of the observed measurements}}{\text{Number of observations}}$$

Median is the observed measurement at which point half the observations are larger and half the observations are smaller (50th percentile).

Mode is the most frequently occurring value in a set of observations.

For example, if we used a data set of the number of haircuts in the past year in a 3rd grade class of 11 students: 1 2 3 3 3 5 6 6 7 9 14.

$$\text{Mean} = \frac{1+2+3+3+3+5+6+6+7+9+14}{11} = 5.4$$

Median = 5

Mode = 3

Normal Distribution

Normal distribution is **continuous frequency distribution of infinite range**, defined by a specific mathematical function with the following properties:

- A continuous, symmetrical distribution; both tails extend to infinity
- Arithmetic mean, mode, and median are identical
- Shape is completely determined by the mean and standard deviation
- Also called Gaussian distribution or "bell-shaped" curve

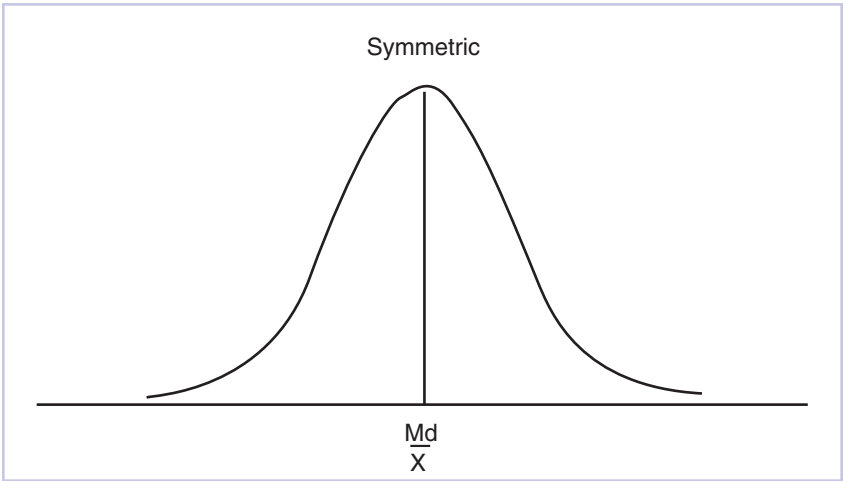


Figure II-21-1. Measures of Center

Note

If a distribution is skewed, increasing the sample size will not affect the "skewness."

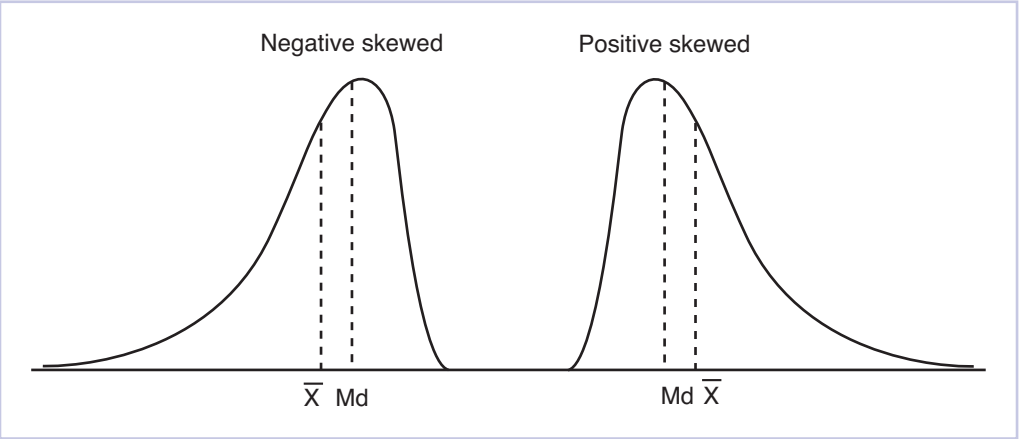


Figure II-21-2. Skewed Distribution Curves

Negative skewed is also called left skewed tail (in the negative direction). Mean is less than median. **Positive skewed** is also called right skewed tail (in the positive direction). Mean is greater than the median.

Dispersion of Data

The dispersion of data helps us identify the spread, or the variation, of a data set.

Range is the difference between the largest and smallest values in a distribution.

Variance is a measure of the variation shown by a set of observations, defined by the sum of the squares of deviations scores of each value divided by the number of degrees of freedom in the set of observations or n – 1.

Standard deviation (s or sd) is the most widely used measure of dispersion of a frequency distribution. It is equal to the positive square root of the variance. Whereas the **mean tells where the group of values are centered**, the **standard deviation is a summary of how widely dispersed the values are around the center**.

$$s = \sqrt{\frac{\sum(X - \overline{X})^2}{n - 1}}$$

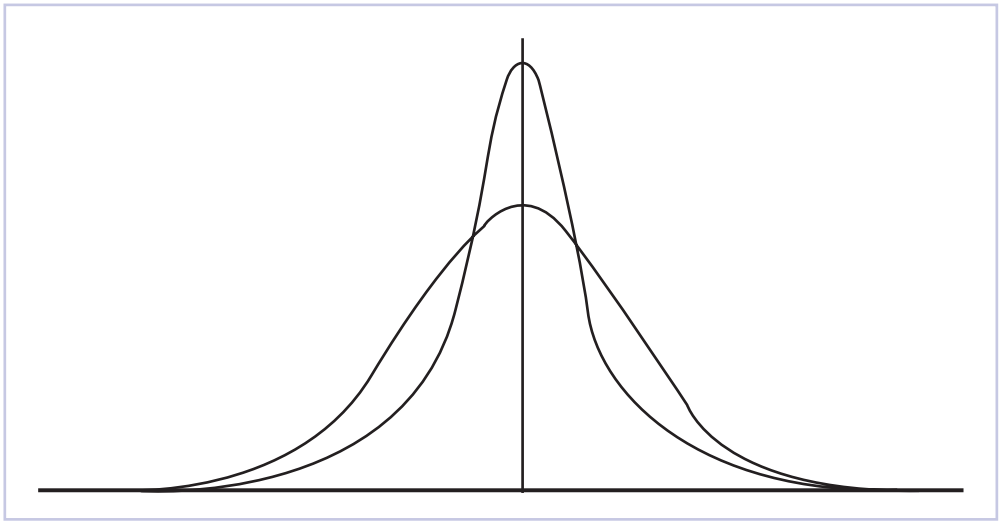


Figure II-21-3. Comparison of 2 Normal Distributions with the Same Means, but Different Standard Deviations

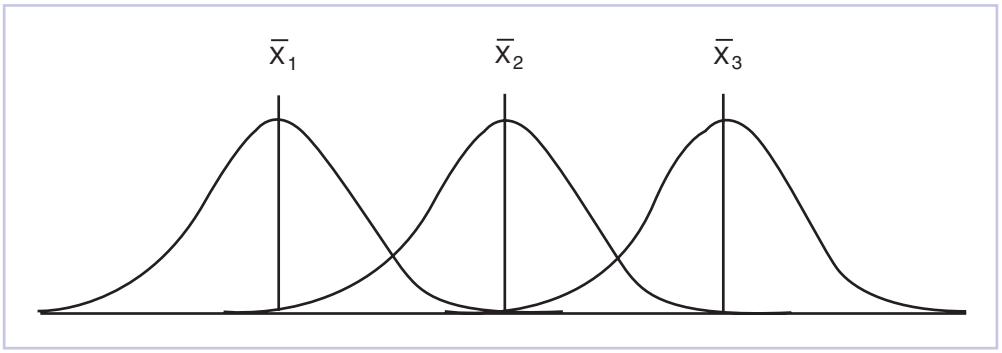


Figure II-21-4. Comparison of 3 Normal Distributions with the Same Standard Deviations, but Different Means

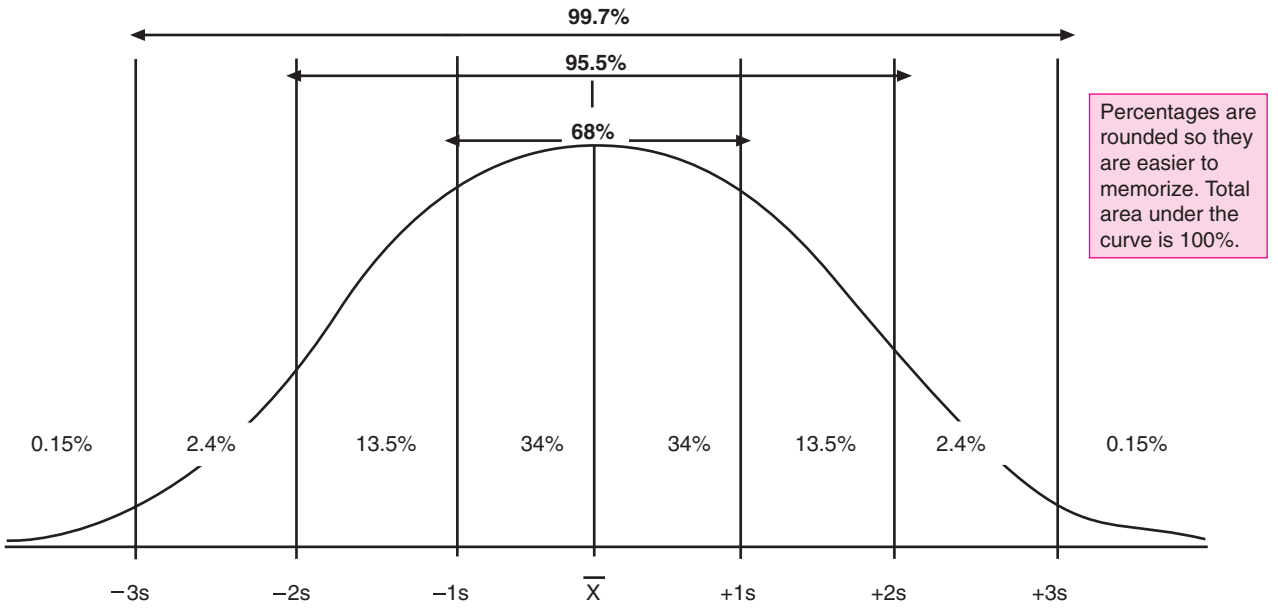


Figure II-21-5. Percentage of Cases within 1, 2, and 3 Standard Deviations of the Mean in a Normal Distribution

The sd is stated in score units. The normal curve has the property that within 1 sd a certain proportion of the cases is included. The property is as follows:

- Between the mean and the value of 1 sd from the mean in either direction, there will be 34% of the cases; there will be 68% of the cases between the score at 1 sd above and 1 sd below the mean.
- Within 2 sd of the mean are 95.5% of the cases.
- Between 1 sd and 2 sd from the mean in either direction, there will be 13.5% of the cases, or 27% for both.
- Within 3 sd of the mean are 99.7% of the cases.
- And between 2 sd and 3 sd from the mean there will be almost 2.5% of the cases, 4.7% for the two extremes together.

There will be a few cases, of course, 0.3%, beyond 3s from the mean both above and below the mean.

You must know these figures for the exam. For example: What percentage of the cases are below 2s below the mean? (2.5%)

Note

On the exam you will not be asked to calculate sd and variance, but you must know what they are and how they relate to the normal curve.

INFERENTIAL STATISTICS

Since investigators are not able to study all members of a population, they must select a sample from which to study and use results to make an estimate for the larger population. To make the best estimate, attempts are made to select a sample that is representative of the

larger population; however, because it is only a sample, estimates may be off. Inferential statistics helps us to assess how uncertain we are about our results, i.e., how confident are we that the result from our sample truly reflects the overall population. It also allows us to say how likely it is that our results occurred only by random chance, rather than being a true reflection of the population.

Confidence Intervals

Confidence intervals are a way of admitting that any measurement from a sample is only an estimate of the population. Although the estimate given from the sample is likely to be close, the true values for the population may be above or below the sample values.

Confidence interval of the mean

The confidence interval is calculated with 2 parts: the Z score and the standard error. The confidence interval of the mean can be calculated as follows:

$$\textbf{Mean} \pm \textbf{Z-score} \times \textbf{standard error of the mean} = \bar{X} \pm Z\left(S/\sqrt{\frac{\sum(X-\bar{X})^2}{n-1}}\right)$$

Standard error of the mean is the standard deviation divided by the square root of the sample size. It represents how much the sample mean may deviate from the true population mean.

- If the sd is larger, the chance of error in the estimate is greater.
- If the sample size is larger, the chance of error in the estimate is less.

The **Z-score or sd score** is a score from a normal distribution with a mean of 0 and a standard deviation of 1. Any distribution can be converted into a Z-score distribution using the formula:

$$Z = \frac{\bar{X} - X}{S}$$

$$Z = \frac{\textbf{Sample mean} - \textbf{population mean}}{\textbf{Standard deviation}}$$

The Z-score distribution is easy to use for calculations because it has simple values. All points in a Z-score distribution are represented in sd units. **Positive scores are above the mean**, while **negative scores are below the mean**. Therefore, a Z-score of +2.0 is exactly 2 standard deviations above the mean; a Z-score of .1.5 is exactly 1.5 standard deviations below the mean.

Z-scores are used in computing confidence intervals to set the level of confidence. Recall that in a normal distribution, 95.5% of the cases are within 2 standard deviations (2 sd) of the mean. To calculate 95% or 99% confidence intervals, all we need to know is what symmetric Z-score to use to contain exactly 95% and 99% of the cases.

- For 95% confidence = 1.96; for calculation purposes, use **Z-score of 2.0** (most commonly used)
- For 99% confidence = 2.58; for calculation purposes, use **Z-score of 2.5**

The more confidence desired, the wider the interval becomes. Therefore, a 99% confidence interval will always be wider than a 95% interval.

Confidence intervals for RR and odds ratios

If the given confidence interval contains 1.0, then there is no statistically significant effect of exposure. For example:

Relative Risk	95% Confidence Interval	Interpretation
1.57	(1.1–2.25)	Statistically significant (increased risk); 57% increased risk with the intervention
1.65	(0.89–2.34)	Not statistically significant (risk is the same); the confidence interval includes 1 (null value)
0.76	(0.56–0.93)	Statistically significant (decreased risk); 24% reduced risk with the intervention

Hypothesis Testing

A hypothesis is a statement that postulates a difference between 2 groups. Inferential statistics is used to evaluate the possibility that this difference occurred by chance.

- **Null hypothesis** says the findings are the **result of chance or random factors**. If you want to show that a drug works, the null hypothesis will be that the drug does not work. The *p*-value (see below) is the chance of getting the result assuming the null hypothesis is true.
  - **One-tailed, i.e., directional** or 1-sided such that one group is greater than or less than the other. For example, Group A is not < Group B, or Group A is not > Group B.
  - **Two-tailed, i.e., nondirectional** or 2-sided such that 2 groups are not the same. For example, Group A = Group B (most commonly used).
- **Alternative hypothesis** says what is left after defining the null hypothesis. In this example, the drug actually does work.

To test your hypothesis, you would draw a random sample from a population (e.g., men with hypertension) make observations on the data of interest (e.g., blood pressure), perform a statistical test, and make an inference. For example, the mean systolic blood pressure of hypertensive men who also smoke was x1 = 161. The mean systolic blood pressure of hypertensive men who do not smoke was x2 = 155. The difference between means of these groups is therefore x1 – x2 = 6, and you can apply a statistical test to decide whether this difference is statistically significant.

Interpretation

p-value

Both the *p*-value and alpha level symbolize significance, and they are very similar (usually set at 0.05).

They are only slightly different in that *p*-value measures the strength or magnitude (i.e., significance) of the data against the null hypothesis, whereas alpha level represents risk and is independent of data.

A *p*-value is used to interpret output from a statistical test; focus on the *p*-value. The *p*-value refers to 2 things: first, it is a standard against which we compare our results, and second, it is a result of computation. The **computed *p*-value is compared with the *p*-value criterion to**

test statistical significance. If the computed value is less than the criterion, we have achieved statistical significance. In general, the smaller the p the better. The *p*-value of a **1-sided t test is exactly half the *p*-value of a 2-sided t test**. One-sided t tests are not commonly used.

The *p*-value criterion is traditionally set at $p \leq 0.05$. (Assume that these are the criteria if no other value is explicitly specified.) Using this standard:

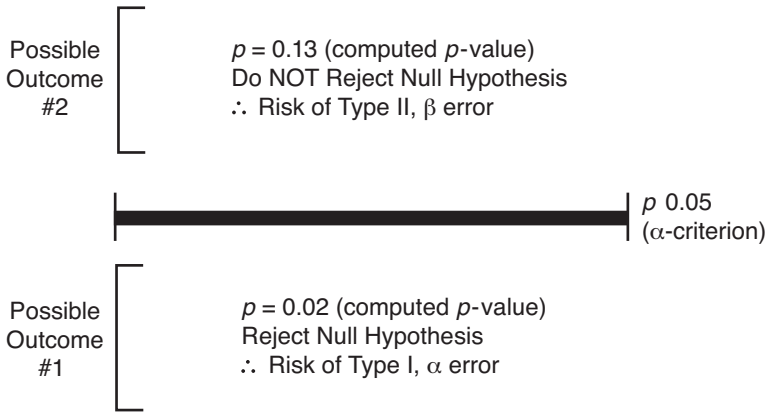


Figure II-21-6. Making Decisions Using *p*-Values

- If $p \leq 0.05$, reject the null hypothesis (reached statistical significance).
- If $p > 0.05$, do not reject the null hypothesis (has not reached statistical significance).

Therefore:

- If $p = 0.13$, fail to reject the null hypothesis, i.e., decide that the drug does not work.
- If $p = 0.02$, reject the null hypothesis, i.e., decide that the drug works.

Types of error

Just because we reject the null hypothesis, we are not certain that we are correct. For some reason, the results given by the sample may be inconsistent with the full population. If this is true, any decision we make on the basis of the sample could be in error. There are 2 types of error we could make:

- **Type I error** (α error): **rejecting the null hypothesis when it is really true**, i.e., assuming a statistically significant effect on the basis of the sample when there is none in the population or asserting that the drug works when it does not.
  - The chance of a type I error is given by the *p*-value. If *p* (or *a*) = 0.05, then the chance of a Type I error is 5 in 100, or 1 in 20.
- **Type II error** (β error): failing to reject the null hypothesis when it is really false, i.e., declaring no significant effect on the basis of the sample when there really is one in the population or asserting the drug does not work when it really does.
  - The chance of a Type II error cannot be directly estimated from the *p*-value.

The alpha level criterion can also be considered the probability of making a type I error. The alpha level criterion is set up in advance of the test. Beta is the probability of making a type II error.

Note

For odds ratio and relative risk, the **null value = 1**.

Power is the capacity to detect a difference if there is one. Increasing sample size (n) increases power. The **general standard for power in a study is 80% or greater**.

Power = 1-beta

When a study with **low power finds a non-statistically significant result**, it is difficult to interpret, i.e., perhaps the study was not designed with enough power to detect a difference. The study result is then better termed inconclusive. In other words, when a study with higher power finds no association, one is more confident with the results of the study.

Meaning of the *p*-value

- Provides criterion for making decisions about the null hypothesis
- Quantifies the chances that a decision to reject the null hypothesis will be wrong
- Tells statistical significance, not clinical significance or likelihood of benefit
- Generally, *p*-value is considered statistically significant if it is equal to or less than 0.05.

Limits to the *p*-value

- Does not tell us the chance that an individual patient will benefit
- Does not tell us the percentage of patients who will benefit
- Does not tell us the degree of benefit expected for a given patient

Types of Scale

To convert the world into numbers, we use 4 types of scale: nominal, ordinal, interval, and ratio scales.

Table II-21-1. Types of Scales in Statistics

Type of Scale	Description	Key Words	Examples
Nominal (Categorical)	Different groups	This or that	Gender, comparing among treatment interventions
Ordinal	Groups in sequence	Comparative quality, rank order	Olympic medals, class rank in medical school
Interval	Exact differences among groups	Quantity, mean, and standard deviation	Height, weight, blood pressure, drug dosage
Ratio	Interval + true zero point	Zero means zero	Temperature measured in degrees Kelvin

A **nominal scale** puts people into boxes without specifying the relationship between the boxes. Gender is a common example, with 2 groups: male and female. Any time you can say it's either this or that, you are dealing with a nominal scale.

Numbers can also be used to express **ordinal** or rank-order relations. For example, we say Ben is taller than Fred. Now we know more than just the category in which to place someone.

We know something about the relationship between the categories (quality). What we do not know is how different the 2 categories are (quantity). Class rank in medical school and medals at the Olympics are examples of ordinal scales.

An **interval scale** (or numeric scale) uses a scale graded in equal increments. In the scale of length, we know that 1 inch is equal to any other inch. Interval scales allow us to say not only that two things are different, but by how much. If a measurement has a mean and a standard deviation, treat it as an interval scale.

The best measure is the **ratio scale**. This scale orders things and contains equal intervals, as do the previous 2 scales, but it has one additional quality: a true zero point. In a ratio scale, zero is a floor, i.e., you cannot go any lower. Measuring temperature using the Kelvin scale yields a ratio scale measurement.

SELECTING A STATISTICAL TEST

Table II-21-2. Types of Scales and Basic Statistical Tests

	Variables		
Name of Statistical Test	Interval	Nominal	Comment
Pearson Correlation	2	0	Is there a linear relationship?
Chi-square	0	2	Any # of groups
t-test	1	1	2 groups only
One-way ANOVA	1	1	2 or more groups
Matched pairs *t*-test	1	1	2 groups, linked data pairs, before and after
Repeated measures ANOVA	1	1	More than 2 groups, linked data

Meta-analysis is a statistical way of **combining the results of many studies** to produce one overall conclusion. It is a mathematic literature review.

Correlation Analysis (r, ranges from –1 to +1)

A **positive value** means that 2 variables go together in the same direction, e.g., MCAT scores have a positive correlation with medical school grades. A **negative value** means the presence of one variable is associated with the absence of another variable, e.g., there is a negative correlation between age and quickness of reflexes.

- The further from zero, the stronger the relationship (r = 0).
- A zero correlation means that 2 variables have no linear relation to one another, e.g., height and success in medical school.

There are 2 types of correlation:

- **Pearson correlation** compares 2 interval level variables.
- **Spearman correlation** compares 2 ordinal level variables.

Correlation, by itself, does not mean causation. A correlation coefficient indicates the degree to which 2 measures are related, not why they are related.

Correlation does not mean that one variable necessarily causes the other.

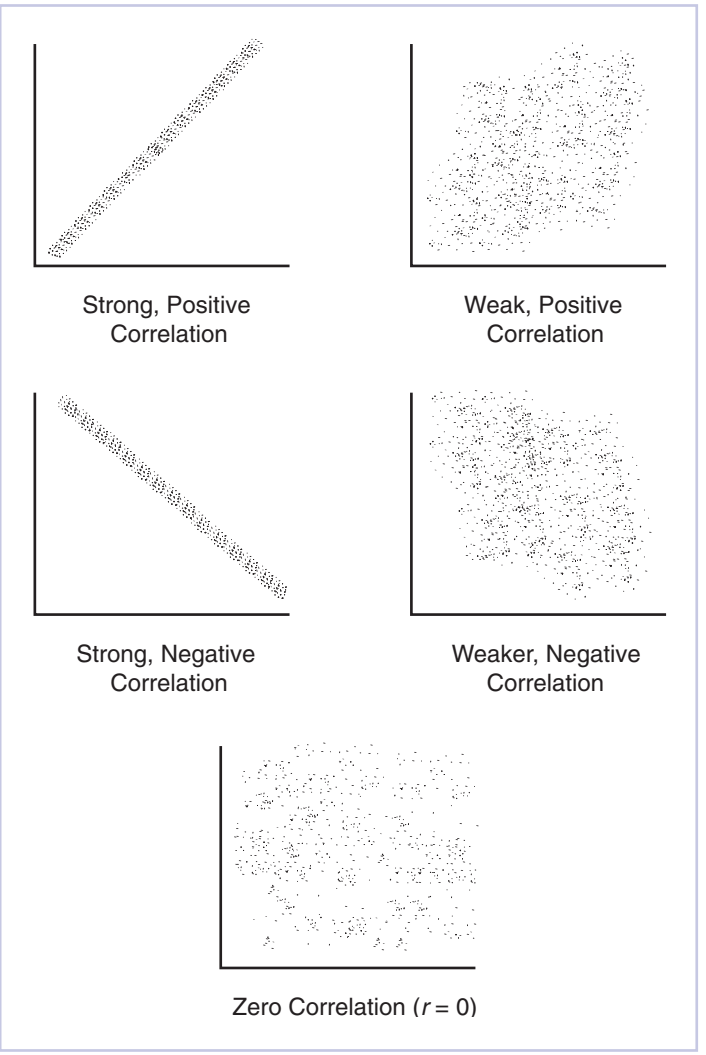


Figure II-21-7. Scatterplots and Correlations

To graph a correlation using a scatterplot, know that a scatterplot will show points that approximate a line. Be able to interpret scatterplots of data: positive slope, negative slope, and which of a set of scatterplots indicates a stronger correlation.

t-Tests

A t-test is used to compare the mean values of continuous data between 2 groups. The output of a t-test is a t-statistic, which is converted to a *p*-value. It is used for 2 groups only, i.e., compares 2 means. For example, do patients with MI who are in psychotherapy have a reduced length of convalescence compared with those who are not in therapy?

- **Pooled t-test**: regular t-test, assuming the variances of the 2 groups are the same
- **Matched pairs t-test**: if each person in one group is matched with a person in the second; applies to before and after measures and linked data

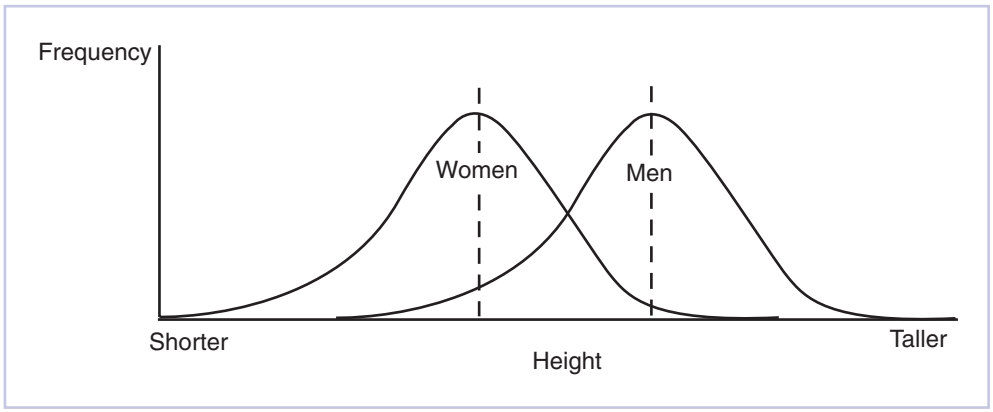


Figure II-21-8. Comparison of the Distributions of 2 Groups

Analysis of Variance

Output from an analysis of variance (ANOVA) is one or more "F" statistic, which is converted to a *p*-value.

- **One-way** compares means of many groups (2+) of a single nominal variable using an interval variable. Significant *p*-value means that at least 2 of the tested groups are different.
- **Two-way** compares means of groups generated by 2 nominal variables using an interval variable. Can test effects of several variables at the same time.
- Repeated measures ANOVA: multiple measurements of same people over time

Chi-Square

Chi-square tests to see whether 2 nominal variables are independent, e.g., testing the efficacy of a new drug by comparing the number of recovered patients given the drug with those who are not.

- Nominal data (or categorical data) only
- Any number of groups

Chi-square is an example of nonparametric test. T test is an example of parametric test, i.e., it involves scores or measurements that come from **normal distributions**. Nonparametric testing is used for categorical data.

Table II-21-3. Chi-Square Analysis for Nominal Data

	New Drug	Placebo	Totals
Recovered	45	35	80
Not Recovered	15	25	40
Totals	60	60	120

Practice Questions

1. The American Medical Association commissions a health study of a representative sample of U.S. physicians. Enrolled physicians complete detailed surveys and undergo an extensive battery of medical tests. For a number of analyses, physicians are classified by subspecialty. Although numerous physiologic measures are assessed, the following questions describe analyses of just one of these, mean fasting plasma glucose. Select the appropriate statistical test for a comparison of mean fasting plasma glucose values for representative samples of surgeons and cardiologists.

   A. *t*-test
   B. Matched pairs *t*-test
   C. One-way ANOVA
   D. Two-way ANOVA
   E. Chi-square

2. An experimenter conducts a test of a new medication compared with the current standard medication. Alpha is selected to be 0.05. At the conclusion of the trial, the sample of patients receiving the new medication shows more improvement than the comparison group on the standard medication. The *p*-value is 0.002. What will the experimenter conclude?

   A. Do not reject the null hypothesis.
   B. The new medication has more clinical benefits than the standard medication.
   C. The likelihood that a type I error has actually been committed is less than the maximum risk the experimenter was willing to accept.
   D. The result is not significant.
   E. A type II error has been committed.

3. Body mass index (BMI) is found to correlate to the following physiologic measures. For which measure is the correlation the strongest?

   A. Physical activity ($r = -0.56$)
   B. Percentage of calories from complex carbohydrates ($r = -0.32$)
   C. Systolic blood pressure ($r = +0.43$)
   D. Triglycerides ($r = +0.37$)
   E. LDL cholesterol ($r = +0.49$)

4. A new treatment for elevated cholesterol is piloted on a sample of 100 men, ages 45–59 with total serum cholesterol in the range of 260–299 mg/dL at entry. Following 3 months on the medication, the mean cholesterol for the treatment group was 250 mg/dL with a standard deviation of 20 mg/dL. What is the 95% confidence interval on the mean for this study?

   A. 210–290 mg/dL
   B. 230–270 mg/dL
   C. 246–254 mg/dL
   D. 248–252 mg/dL
   E. 249–251 mg/dL

Practice Questions

5. The Wechsler Adult Intelligence Scale–Revised (WAIS-R) is a standardized IQ test with a mean of 100 and a standard deviation of 15. A person with an IQ of 115 is at what percentile of IQ?

   A. 50th
   B. 68th
   C. 84th
   D. 95th
   E. 99th

6. From a published article describing the results of the study presented above, the following data table is abstracted. This table presents the relative risks (RR) of clinical diabetes for each of the categories of fat intake relative to the baseline category of <20%. Interpret the study findings from the tabular data.

	% of Calories from Fat	RR for Diabetes	95% Confidence Interval
Baseline	‹20	1	——
Level 2	20–34	1.3	0.8–1.8
Level 3	35–49	2	1.6–2.6
Level 4	›50	3	2.7–3.3

   A. Levels 2, 3, and 4 have significantly elevated risks for diabetes relative to baseline.
   B. Levels 2 and 3 are significantly different from each other.
   C. Levels 3 and 4 are significantly different from baseline and risk elevating.
   D. Levels 3 and 4 are not significantly different from each other.
   E. RR for levels 2, 3, and 4 are numerically different but not significantly different from baseline.

1. **Answer: A**. T test is used to compare means of glucose levels in these 2 groups. ANOVA is used for 3+ groups.
2. **Answer: C**. *P* value <0.05 (less than 1 in 20) is the probability of obtaining this result based on chance alone assuming the null hypothesis is true.
3. **Answer: A**. R = –0.56 has the strongest negative correlation of the choices. Choose the number closest to –1.0 or +1.0.
4. **Answer: C**. 95% confidence interval can be estimated by mean + or –2* (standard deviation/ square root n) 2*(20/square root 100) = 2*(20/10) = 4. 250 + or – 4 = 246 to 254 mg/dL
5. **Answer: C**.
6. **Answer: C**. Level 2 confidence intervals contain 1 (not statistically significant). Level 3 and 4 confidence intervals do not contain 1 (statistically significant).

Ethics 22

Learning Objectives

- Identify some important Supreme Court cases related to medical ethics, and explain their significance
- Distinguish between the ethical and legal principles, and explain how they affect medical practice

SELECTED IMPORTANT COURT CASES

Karen Ann Quinlan: Substituted Judgment Standard

In the Quinlan case, Karen Ann was in a persistent vegetative state, being kept alive only by life support. Karen's father asked to have her life support terminated according to his understanding of what Karen Ann would want. The court found that "if Karen herself were miraculously lucid for an interval . . . and perceptive of her irreversible condition, she could effectively decide upon discontinuance of the life support apparatus, even if it meant the prospect of natural death."

The court therefore allowed termination of life support, not because the father asked, but because it held that the father's request was most likely the expression of Karen Ann's own wishes.

Substituted judgment begins with the premise that decisions belong to the competent patient by virtue of the rights of autonomy and privacy. In this case, however, the patient is unable to decide, and a decision-maker who is the best representative of the patient's wishes must be substituted. In legal terms, the patient has the right to decide but is incompetent to do so. Therefore, the decision is made for the patient on the basis of the best estimate of his or her subjective wishes.

The key here is *not* who is the closest next of kin, but who is most likely to represent the patient's own wishes.

Brother Fox *(Eichner vs Dillon)*: Best Interest Standard

The New York Court of Appeals, in its decision of *Eichner vs Dillon,* held that trying to determine what a never-competent patient would have decided is practically impossible. Obviously, it is difficult to ascertain the actual (subjective) wishes of incompetents.

Therefore, if the patient has always been incompetent, or no one knows the patient well enough to render substituted judgment, the use of substituted judgment standard is questionable, at best.

Under these circumstances, decisions are made for the patient using the **best interest standard**. The object of the standard is to decide what a hypothetical "reasonable person" would decide to do after weighing the benefits and burdens of each course of action.

Note here the issue of who makes the decision is less important. All persons applying the best-interest standard should come to the same conclusions.

Infant Doe: Foregoing Lifesaving Surgery, Parents Withholding Treatment

As a general rule, parents cannot withhold life- or limb-saving treatment from their children. Yet, in this exceptional case they did.

Baby Boy Doe was born with Down syndrome (trisomy 21) and with a tracheo-esophageal fistula. The infant's parents were informed that surgery to correct his fistula would have "an even chance of success." Left untreated, the fistula would soon lead to the infant's death from starvation or pneumonia. The parents, who also had 2 healthy children, chose to withhold food and treatment and "let nature take its course."

Court action to remove the infant from his parents' custody (and permit the surgery) was sought by the county prosecutor. The court denied such action, and the Indiana Supreme Court declined to review the lower court's ruling. Infant Doe died at 6 days of age, as Indiana authorities were seeking intervention from the U.S. Supreme Court.

This case is simply an application of the best-interest standard. The court agreed with the parents that the burdens of treatment far outweighed any expected benefits.

Roe vs Wade (1973): The Patient Decides

Known to most people as the "abortion legalizing decision," the importance of this case is not limited to its impact on abortion.

Faced with a conflict between the rights of the mother versus the rights of the putative unborn child, the court held that in the first trimester, the mother's rights are certainly paramount, and that states may, if they wish, have the mother's rights remain paramount for the full term of the pregnancy.

Because the mother gets to decide, even in the face of threats to the fetus, by extension, all patients get to decide about their own bodies and the health care they receive. In the United States, the locus for decision-making about health care resides with the patient, not the physician.

Note that courts have held that a pregnant woman has the right to refuse care (e.g., blood transfusions) even if it places her unborn child at risk.

Tarasoff Decision: Duty to Warn and Duty to Protect

A student visiting a counselor at a counseling center in California states that he is going to kill someone. When he leaves, the counselor is concerned enough to call the police but takes no further action. The student subsequently kills the person he threatened. The court found the counselor and the center liable because they did not go far enough to warn and protect the potential victim.

The counselor should have called the police and then should also have tried in every way possible to notify the potential victim of the potential danger.

In similar situations, first try to detain the person making the threat, next call the police, and finally notify and warn the potential victim. All 3 actions should be taken, or at least attempted.

LEGAL ISSUES RELATED TO MEDICAL PRACTICE

This section lays out a set of rules that constitute the general consensus of legal opinion. Apply these rules to individual situations as they arise.

Rule #1: Competent patients have the right to refuse medical treatment.

Incompetent patients have the same rights, but must be exercised differently (via a surrogate).

- Patients have an almost absolute right to refuse. Patients have almost absolute control over their own bodies. The sicker the patient, the lesser the chance of recovery, the greater the right to refuse treatment.

Rule #2: If a patient is incompetent to make decisions, the physician may rely on advance directives.

Advance directives can be oral.

- Living will: written document expressing wishes
  - Care facilities must provide information at time of admission.
  - Responsibility of the institution, not the physician
  - Only applies to end-of-life care
- Health power of attorney: designating the surrogate decision-maker
  - "Speaks with the patient's voice"
  - Beats all other decision rules
- In end-of-life circumstances, if power of attorney person *directly* contradicts the living will, follow the living will.

Rule #3: Assume the patient is competent unless clear behavioral evidence indicates otherwise.

Competence is a legal, not a medical issue.

- A diagnosis, by itself, tells you little about a patient's competence.
- Clear behavioral evidence would be:
  - Patient is grossly psychotic and dysfunctional
  - Patient's physical or mental state prevents simple communication
- If you are unsure, assume the patient is competent. The patient does not have to prove to you that he is competent. You have to have clear evidence to assume that he is not.

Rule #4: When surrogates make decisions for a patient, they should use the following criteria and in this order:

- Subjective standard
  - Actual intent, advance directive
  - What did the patient say in the past?
- Substituted judgment
  - Who best represents the patient?
  - What would patient say if he or she could?
- Best-interest standard
  - Burdens versus benefits
  - Interests of patient, not preferences of the decision-maker

Note

Family matters only to the degree that reflects the patient's wishes. Family's own wishes are not relevant.

Rule #5: Feeding tube is a medical treatment and can be withdrawn at the patient's request.

A feeding tube is not considered killing the patient, but rather stopping treatment at a patient's request.

- A competent person can refuse even lifesaving hydration and nutrition.

Rule #6: Do nothing to actively assist the patient to die sooner.

Active euthanasia and assisted suicide are on difficult ground.

- Passive, i.e., allowing to die = OK
- Active, i.e., killing = NOT OK

On the other hand, do all you can to reduce the patient's suffering (e.g., giving pain medication).

Rule #7: The physician decides when the patient is dead.

If the physician thinks continued treatment is futile (the patient has shown no improvement) but the surrogate insists on continued treatment, the treatment should continue. If there are no more treatment options (the patient is cortically dead) and the family insists on treatment, there is nothing the physician can do; treatment must stop.

Rule #8: Never abandon a patient.

Lack of financial resources or lack of results are never reasons to stop treatment of a patient. An annoying or difficult patient is still your patient; you cannot ever threaten abandonment.

Rule #9: Keep the physician/patient relationship within bounds.

Intimate social contact with anyone who is or has been a patient is prohibited. AMA guidelines say, "for at least 2 years."

- Do not date parents of pediatric patients or children of geriatric patients.
- Do not treat friends or family.
- Do not prescribe for colleagues unless a physician/patient relationship exists.
- If patients are inappropriate, gently but clearly let them know what acceptable behavior would be.
- Any gift from a patient beyond a small token should be declined.

Rule #10: Stop harm from happening.

Beyond "do no harm," you must stop anyone from hurting himself or others. Take whatever action is required to prevent harm.

- Harm can be spreading disease, physical assault, psychological abuse, neglect, infliction of pain, or anything that produces notable disress.
- You must also protect your patient, or anyone not your patient, from being hurt by another.

Rule #11: Always obtain informed consent.

Full, informed consent requires that the patient has received and understood 5 pieces of information:

  - Nature of procedure
  - Purpose or rationale
  - Benefits
  - Risks
  - Availability of alternatives

There are 4 exceptions to informed consent:

  - Emergency
  - Waiver by patient
  - Patient is incompetent
  - Therapeutic privilege (unconscious, confused, physician deprives patient of autonomy in interest of health)

- Gag clauses that prohibit a physician from discussing treatment options that are not approved violate informed consent and are illegal.
- Consent can be oral.
- A signed paper the patient has not read or does not understand does NOT constitute informed consent.
- Written consent can be revoked orally at any time.

Rule #12: Special rules apply with children.

Children younger than 18 years are minors and are legally incompetent.

- Exceptions: emancipated minors
  - If older than 13 years and taking care of self, i.e., living alone, treat as an adult.
  - Marriage makes a child emancipated, as does serving in the military.
  - Pregnancy or giving birth, in most cases, do not.
- Partial emancipation
  - Many states have special ages of consent: generally age 14 and older
  - For certain issues only:
    - Substance drug treatment
    - Prenatal care
    - Sexually transmitted disease treatment
    - Birth control

Rule #13: Parents cannot withhold life- or limb-saving treatment from their children.

If parents refuse permission to treat child, use the following guidelines:

- If immediate emergency, go ahead and treat.
- If not immediate, but still critical (e.g., juvenile diabetes), generally the child is declared a ward of the court and the court grants permission.
- If not life-or limb-threatening (e.g., child needs minor stitches), listen to the parents.

Note that the child cannot give permission. A child's refusal of treatment is irrelevant.

Rule #14: For the purposes of the exam, issues governed by laws that vary widely across states cannot be tested.

This includes elective abortions (minor and spousal rights differ by locality) and legal age for drinking alcohol (vary by state).

Rule #15: Good Samaritan Laws limit liability in nonmedical settings.

- Not required to stop to help
- If help offered, shielded from liability provided:
  - Actions are within physician's competence.
  - Only accepted procedures are performed.
  - Physician remains at scene after starting therapy until relieved by competent personnel.
  - No compensation changes hands.

Rule #16: Confidentiality is absolute.

Physicians require a patient's permission to reveal any personal information. Additionally, physicians must try to ensure that the patient's information is not accessible to others.

- Getting a consultation is permitted, as the consultant is bound by confidentiality, too. However, watch the location of the consultation. Be careful not to be overheard (e.g., not elevator or cafeteria).
- If you receive a court subpoena, show up in court but do not divulge information about your patient.
- If patient is a threat to self or others, you MUST break confidentiality.
  - Duty to warn and duty to protect (Tarasoff case)
  - A specific threat to a specific person
  - Suicide, homicide, and abuse are obvious threats.
  - Infectious disease should generally be treated as a threat, but be careful. Here issue is usually getting the patient to work with you to tell the person who is at risk.
  - In the case of an STD, the issue is not really whether to inform a sexual partner, but how they should be told. Best advice: Have patient and partner come to your office.

Rule #17: Patients should be given the chance to state DNR (Do Not Resuscitate) orders, and physicians should follow them.

- Continue with ongoing treatments.
- Most physicians are unaware of DNR orders.
- DNR decisions are made by the patient or surrogate.
- Have DNR discussions as part of your first encounter with the patient.
- Do not ask the patient about "do not resuscitate" wishes. Explain what is entailed.

Note

DNR refers only to cardiopulmonary resuscitation.

Rule #18: Committed mentally ill patients retain their rights.

Committed mentally ill adults legally are entitled to the following:

- They must have treatment available.
- They can refuse treatment.
- They can command a jury trial to determine "sanity."

- They lose only the civil liberty to come and go.
- They retain their competence for conducting business transactions, marriage, divorce, voting, driving.
- The words "sanity" and "competence" are legal, not psychiatric, terms. They refer to prediction of dangerousness, and medicopsychological studies show that health care professionals cannot reliably and validly predict such dangerousness.

Rule #19: Detain patients to protect them or others.

Emergency detention can be effected by a physician and/or a law enforcement person for 48 hours, pending a hearing. A physician can detain; only a judge can commit. With children, special rules exist. Children can be committed only if:

- They are in imminent danger to self and/or others.
- They are unable to care for their own daily needs.
- The parents have absolutely no control over the child, and the child is in danger (e.g., fire-setter), but not because the parents are unwilling to discipline a child.

Rule #20: Remove from patient contact any health care professionals who pose a risk to patients.

The patient, not professional solidarity, comes first.

- Types of risks
  - Infectious disease (TB)
  - Substance-related disorders
  - Depression (or other psychological issues)
  - Incompetence
- Actions
  - Insist that they take time off
  - Contact their supervisors if necessary

Rule #21: Focus on what is the best ethical conduct, not simply the letter of the law.

The best answers are those that are both legal and ethical.

Practice Questions

- Should physicians answer questions from insurance companies or employers? (Not without a release from the patient)
- Should physicians answer questions from the patient's family without the patient's explicit permission? (No)

- What information can the physician withhold from the patient? (Nothing. If patient may react negatively, figure out how to tell patient to mitigate negative outcome.)
- What if the family requests that certain information be kept from the patient? (Tell the patient, but first find out why they don't want the patient told.)
- Who owns the medical record? (Health care provider, but patient must be given access or copy upon request)

What should the physician do in each of these situations?

- Patient refuses lifesaving treatment on religious grounds? (Don't treat)
- Wife refuses to consent to emergency lifesaving treatment for unconscious husband citing religious grounds? (Treat, no time to assess substituted judgment)
- Wife produces card stating unconscious husband's wish to not be treated on religious grounds? (Don't treat)
- Mother refuses to consent to emergency lifesaving treatment for her daughter on religious grounds? (Treat)
- What if the child's life is at risk, but the risk is not immediate? (Court takes guardianship)
- From whom do you get permission to treat a girl who is 17 years old? (Her guardian)

From whom does the physician obtain consent in each case?

- A 17-year-old girl's parents are out of the country and the girl is staying with a babysitter? (If a threat to health, the physician can treat under doctrine of *in locum parentis*)
- A 17-year-old girl who has been living on her own and taking care of herself? (The girl herself)
- A 17-year-old girl who is married? (The girl herself)
- A 17-year-old girl who is pregnant? (Her guardian)
- A 16-year-old daughter refuses medication but her mother consents, do you write the prescription? (Yes)
- The 16-year-old daughter consents, but the mother refuses? (No)
- The mother of a minor consents, but the father refuses? (Yes, only one permission needed)
- When should the physician provide informed consent? (Always)
- Must informed consent be written? (No)
- Can written consent be revoked orally? (Yes)
- Can you get informed consent from a schizophrenic man? (Yes, unless there is clear behavioral evidence that he is incompetent)
- Must you get informed consent from a prisoner if the police bring in the prisoner for examination? (Yes)

Interpretation of Medical Literature 23

Learning Objectives

- ❑ Critique a journal article, i.e., assess whether appropriate statistical tests were used, what biases or assumptions were inherent in the research study design, and what class of evidence was presented

INTRODUCTION

The purpose of this chapter is to provide you with an approach to reading and understanding research articles and pharmaceutical advertisements. It is based on principles of epidemiology.

An understanding of these concepts is fundamental to the comprehension of medical literature. We have sacrificed depth for brevity since our goal was to provide a few fundamental tools.

Research Abstract 1

Wedge Resection or Lobectomy: Comparison of Tumor Recurrence Rates and Overall Survival in NSCLC Patients Receiving Preoperative Chemotherapy

Wedge resection for non-small-cell lung cancer (NSCLC) stage I patients still remains controversial with many physicians. The primary outcomes of tumor recurrence and overall survival (OS) remain unclear when compared to complete lobectomy, which has traditionally been considered a far more effective procedure. However, a recent compilation of case reports and case series reports have validated impressive tumor recurrence and OS rates that were previously only believed to be seen in patients receiving lobectomy. Our primary objective was to compare and analyze the tumor recurrence rates and OS for both wedge resection and lobectomy in patients with stage 1 NSCLC following preoperative chemotherapy.

Methods

We systematically reviewed individual case reports and case series reports from 152 institutions in the United States for patients who first received preoperative chemotherapy and then underwent either wedge resection (248 patients) or lobectomy (329 patients). A propensity score algorithm was used to reduce the confounding that can occur when examining the effects and variables related to both treatment measures. Following the procedures, tumor recurrence and OS was assessed at 3 and 5 years in all patients.

Results

Preoperative mortality related to chemotherapy complications for patients scheduled to have wedge resection or lobectomy was 0.8% and 1.5%, respectively ($p = 0.22$). Perioperative mortality in patients undergoing lobectomy was 3.8% versus 0.8% in those receiving wedge resection ($p = 0.02$). During the predetermined follow-up times at 3 and 5 years, overall tumor recurrence (both locoregional and metastases) were assessed:

At the 3 year follow-up, overall tumor recurrence was 5.9% for wedge resection and 4.2% for lobectomy ($p = 0.41$).

At the 5-year follow-up, overall tumor recurrence was 6.3% for wedge resection and 6.1% for lobectomy ($p = 0.29$).

When comparing the OS for wedge resection with lobectomy the 3-year OS rates were 82% vs. 71%, respectively; ($p = .09$) and 5-year OS rates were 69% vs. 68%, respectively; ($p = .29$). Wedge resection was not found to be an independent predictor of tumor recurrence (hazard ratio, 1.23; 99% CI, 0.96 to 1.15) or OS (hazard ratio, 1.43; 99% CI, 0.92 to 1.23).

Conclusion

Wedge resection and lobectomy are associated with similar overall tumor recurrence and overall survival rates when performed after preoperative chemotherapy. However, perioperative complications and mortality are significantly lower in patients receiving wedge resection compared to lobectomy. Since patients generally maintain superior overall lung function with wedge resection, we recommended that wedge resection be performed in all eligible patients with Stage 1 NSCLC unless there is a compelling reason to perform a lobectomy.

Practice Questions

1. Information from the abstract most strongly supports which of the following conclusions?

   (A) Both wedge resection and lobectomy have lower mortality and tumor recurrence rates when patients first receive preoperative chemotherapy.

   (B) Perioperative mortality was lower in patients undergoing wedge resection.

   (C) Postoperative complications were lower in patients undergoing wedge resection.

   (D) Pulmonary function tests at 1 year were significantly higher in patients receiving wedge resection.

   (E) The overall survival for wedge resection at 3 years was proven to be higher than that of lobectomy.

The correct answer is choice B. Of the answer choices, choice B is most supported by the information provided in the drug abstract. The statement, "Perioperative mortality was lower in patients undergoing wedge resection" is supported by the data provided in the Results section. We are told that perioperative mortality in those receiving lobectomy was 3.8% versus 0.8% for those receiving wedge resection ($p = 0.02$). This data shows that mortality in those receiving a lobectomy was almost 5x higher than seen in those receiving wedge resection. Furthermore, the *p*-value is 0.02, which shows statistical significance.

The stated objective of the researchers was to "compare and analyze the tumor recurrence rates and OS for both wedge resection and lobectomy in patients with stage I NSCLC following preoperative chemotherapy." In other words, researchers assessed tumor recurrence and OS in patients receiving 2 different surgical procedures. Since all patients received preoperative chemotherapy, one cannot draw a conclusion about the impact of preoperative chemotherapy based on the information presented (**choice A**). Remember, there would have to be a subset of patients who did not receive preoperative chemotherapy in order for a comparative analysis to be performed.

Postoperative complications (**choice C**) were not discussed in the abstract.

A clinician could reasonably conclude that pulmonary function tests would be higher at 1 year in patients receiving wedge resection when compared with lobectomy (**choice D**). However, this "reasonable assumption" is not supported, as data regarding lung function at 1 year was not presented in the abstract.

Choice E states "The overall survival for wedge resection at 3 years was proven to be higher than that of lobectomy." In the Results section of the abstract, it says, "When comparing the OS for wedge resection with lobectomy, the 3-year OS rates were 82% vs. 71%, respectively; ($p = .09$)." At first glance it may appear to be a correct statement; however, the *p*-value is 0.09. Therefore, the 2 percentages are not statistically different.

2. Which of the following best describes the type of study performed?

   (A) Case-control study
   (B) Crossover study
   (C) Meta-analysis
   (D) Propensity-matched analysis
   (E) Randomized, controlled clinical trial

The correct answer is choice D. You are asked to determine what type of study/analysis the researchers performed. The researchers reviewed individual case reports and case series reports from a number of institutions. After reviewing and compiling the data, they used an algorithm to reduce confounding variables and subsequently analyze the data. Based on this information, we can conclude that the researchers performed a **propensity-matched analysis**. Propensity score matching (PSM) is used in the statistical analysis of observational data. PSM is a statistical matching technique which attempts to approximate the effect of a treatment by accounting for the covariates that predict receiving a given treatment. This type of statistical analysis is used to reduce bias caused by confounding variables. Propensity scores (obtained from a propensity-matched analysis) are valuable when attempting to draw causal conclusions from observational studies (such as case reports) where the "treatment" or "independent variable" was not originally randomly assigned.

Case-control studies (**choice A**) are retrospective observational studies used to identify risk factors believed to be associated with a particular disease or condition. Subjects are initially classified as having or not having the disease, and then their histories are explored to identify the presence or absence of any risk factors. Data are usually analyzed by means of an odds-ratio and interpreted such that if something occurs in the history of the diseased group, but not in the non-diseased group, then it will be identified as a risk factor.

Crossover studies (**choice B**) are clinical trials in which 2 comparison groups (for example) both receive the drug being tested and the comparative intervention (often a placebo) at different times. This interventional study will generally begin with one group (group A) receiving the investigational drug while a comparison group (group B) receives a placebo. Then, at some predetermined time, there will be a washout period and then Group A is switched to the placebo, while the Group B is given the investigational drug. This study design allows comparison of those on and off the drug, but also satisfies the ethical requirement that everyone in the study is exposed to whatever benefit the experimental drug may provide.

A meta-analysis (**choice C**) will meticulously examine several interventional clinical studies on a particular disease state (or treatment measure) and then combine the results using an acceptable statistical methodology. The results will be presented as if they were from 1 large study. The classical meta-analysis compares 2 types of treatment measures while multiple treatment meta-analysis (or network meta-analysis) can provide estimates of treatment efficacy of multiple treatment regimens, even when direct comparisons are unavailable. One of the key differences between a meta-analysis and a propensity matched analysis is that a meta-analysis is used with interventional studies, and a propensity-matched analysis is used with observational reports or studies.

A randomized, controlled clinical trial (**choice E**) is a type of interventional study where a researcher will administer a medication or treatment measure to one group of participants and evaluate its effects against a control group who receives another treatment measure or placebo. Subjects in the study are randomly allocated into "intervention" and "control" groups to receive or not receive an experimental preventive or therapeutic procedure or intervention. In the "wedge resection" analysis, researchers compiled the results from several observational

studies. The data evaluated was derived from case reports where patients were NOT originally assigned to receive either a wedge resection or lobectomy.

3. The next step in follow-up of these research results would be to conduct which type of study?

   (A) Case-control study
   (B) Cohort study
   (C) Cross sectional study
   (D) Randomized, controlled clinical trial
   (E) Replication in a different biological model

The correct answer is D. In the current study, researchers reviewed and compiled the data from numerous case reports and case series reports. They then attempted to draw causal conclusions from these observational studies where the treatment was not originally randomly assigned. Using this approach, researchers are able to determine if further investigation is warranted. In this particular analysis, researchers identified a higher than expected overall survival rate and lower than expected tumor recurrence rate associated with a procedure (wedge resection) that is believed to be associated with better postoperative lung function as compared to lobectomy. Since the results of their analysis essentially showed no real difference in overall tumor recurrence rates and overall survival rates, the next step would be to further validate these results with an interventional study, such as a prospective, randomized controlled trial (RCT). In an RCT, researchers will likely randomly assign patients to receive either wedge resection or lobectomy following preoperative chemotherapy. Researchers will then be able to determine if there is a statistical difference between the 2 treatment options.

Case-control studies (**choice A**) are retrospective observational studies used to identify risk factors that are believed to be associated with a particular disease or condition. Subjects are initially classified as having or not having the disease in question, and then their histories are explored to identify the presence or absence of any risk factors.

Cohort studies (**choice B**) are observational studies in which subjects are classified as having or not having a risk factor and then followed forward in time so incidence rates for the 2 groups can be compared. Although cohort studies are a type of prospective study, the next step would be to use an "interventional" prospective study, such as a randomized controlled clinical trial.

Cross sectional studies (**choice C**) are observational studies used to assess the prevalence of a disease in a given population and the factors which co-occur with that disease at a particular time.

Replication in a different model (**choice E**) is a type of study generally used in early animal testing of experimental medications. For example, early animal testing for a new compound may involve a small number of rats. Once data is obtained from a single animal test, there is still a lot of information that needs to be obtained and questions that need answered before this new compound (experimental drug) can be considered for human trials. Therefore, researchers often perform several different types of animal tests using a variety of rat species followed by testing in other animal models.

Research Abstract 2

Mekanib Improved Overall Survival and Decreased Vemurafenib-Resistance in BRAF-mutated Metastatic Melanoma

BRAF mutations have been observed in approximately 50% of all malignant melanomas. The most predominant BRAF mutations found in melanoma are those that introduce an amino acid substitution at valine 600. Approximately 80–90% of these mutations are classified as BRAF V600E. Other predominant BRAF mutations include V600K, V600R, and V600D. All of these mutations result in heightened BRAF kinase activity and amplified phosphorylation of downstream targets, which in particular includes MEK. BRAF inhibitor therapy (with vemurafenib or dabrafenib) is associated with well-documented clinical benefit in most patients with BRAF V600E-mutated melanoma (and other subtypes). However, resistance to these drugs and tumor progression generally occurs in patients within the first year. It is believed that BRAF mutations stimulate melanoma cell proliferation and survival predominantly through activation of MEK. The purpose of this study was to determine if the addition of the allosteric MEK1/MEK2 inhibitor mekanib (KAP071714) to vemurafenib delayed expected vemurafenib resistance as well as improved progression free survival (PFS) and overall survival (OS) in comparison to dacarbazine.

Methods

This was a phase 3, multicenter, double-blinded, randomized clinical trial comparing the effectiveness of mekanib (KAP071714) in 447 total participants with previously untreated, metastatic melanoma with the BRAF V600E mutation. Patients were randomly assigned into 2 cohorts. Cohort A (222 participants): received dacarbazine (1000 mg per square meter of body-surface area intravenously every 3 weeks); Cohort B (225 participants): received vemurafenib (960 mg orally twice daily) + mekanib (150 mg orally daily). PFS was the primary end point and OS was a secondary end point.

Results

Median PFS was 11.6 months in the mekanib group and 2.3 months in the dacarbazine group (hazard ratio for disease progression or death in the mekanib group, 0.23; 95% confidence interval [CI], 0.18 to 0.28; $p<0.007$). At 15 months, the rate of overall survival was 78% in the mekanib group and 42% in the dacarbazine group (hazard ratio for death, 0.43; 95% CI, 0.33 to 0.53; $p = 0.02$). Elevated hepatic enzymes, rash, diarrhea, and hypertension were the most common toxic effects in the mekanib group. Nausea, vomiting alopecia, facial flushing, myalgia, leukopenia, and hepatotoxicity were the most common toxic effects in the dacarbazine group. Eight patients in the mekanib group and 15 patients in the dacarbazine group withdrew from the study due to severe side effects. Secondary skin neoplasms were not observed in either group.

Conclusion

Mekanib, as compared with traditional dacarbazine chemotherapy, improved rates of PFS and OS among patients with the BRAF-mutated metastatic melanoma as well as delayed vemurafenib drug resistance. Mekanib should be considered for use in conjunction with vemurafenib for the treatment of BRAF-mutated metastatic melanoma.

(Funded by SMILE Pharmaceuticals, ClinicalTrials.gov number NCT0123456789101112)

Practice Questions

1. Information from the abstract above most strongly supports which of the following conclusions about mekanib?

   (A) In the treatment of select cases of metastatic melanoma, mekanib alone provides higher rates of PFS and OS than dacarbazine alone.

   (B) Mekanib does not produce severe side effects.

   (C) Mekanib produces fewer side effects than dacarbazine.

   (D) Metastatic melanoma patients with BRAF V600K mutations have improved PFS and OS rates when taking vemurafenib + mekanib versus dacarbazine.

   (E) Most metastatic melanoma patients appropriately prescribed vemurafenib and mekanib are likely to complete their treatment regimen.

The correct answer is choice E. You are being asked to determine which answer choice is most supported by the information provided in the abstract. While several answer choices might "look good," you will be able to eliminate the incorrect answer choices once you examine the meaning of each statement. Of the answer choices, choice E is most supported by the information provided in the drug abstract. The Results section indicates that "Eight patients in the mekanib group and 15 patients in the dacarbazine group withdrew from the study due to severe side effects." Of the 225 patients originally enrolled in the mekanib + vemurafenib arm of the study, 217 persons or 96% of the original study group completed the study. Hence, you can reasonably conclude that most metastatic melanoma patients appropriately prescribed vemurafenib and mekanib are likely to complete their treatment regimen.

The statement, "In the treatment of select cases of metastatic melanoma, mekanib alone provides higher rates of PFS and OS than dacarbazine alone" can be eliminated (**choice A**) since the study was not designed to evaluate mekanib versus dacarbazine. This study evaluated mekanib PLUS vemurafenib versus dacarbazine.

"Mekanib does not produce severe side effects" (**choice B**) is an incorrect statement because the abstract only lists a few of the most common side effects. It does not mention the severe (and less common) side effects. These findings are likely to be found in the body of the published study. Remember, this is an abstract and only provides limited information.

"Mekanib produces fewer side effects than dacarbazine" (**choice C**) is incorrect because the abstract only lists a few of the most common side effects for both drugs. It does not outline the number and frequency of occurrence of side effects. These findings are likely to be found in the complete study.

The statement "Metastatic melanoma patients with BRAF V600K mutations have improved PFS and OS rates when taking vemurafenib + mekanib versus dacarbazine" can be eliminated (**choice D**), because the study was only performed in metastatic melanoma patients with BRAF V600E mutations. Hence, the reader cannot draw conclusions about the effect of vemurafenib plus mekanib in this patient population.

2. In the conclusion section of the abstract, the authors indicate that when mekanib was added to vemurafenib the drug delayed vemurafenib drug resistance. Which of the following is the most likely reason that the reader should question the validity of this claim?

   (A) Insufficient follow-up of study participants
   (B) Insufficient information on adverse effects and drug-drug interactions
   (C) Lack of an appropriate control group
   (D) Subject attrition
   (E) Use of hazard ratio instead of relative risk

The correct answer is choice C. You are asked to determine the most likely reason why one should question the validity of the claim that mekanib delays vemurafenib-resistance. The correct answer is lack of an appropriate control group. In order for researchers to conclude that mekanib decreases vemurafenib resistance, the control group must be vemurafenib alone and the study group must be vemurafenib PLUS mekanib. In this study, the control group was dacarbazine and study group was vemurafenib plus mekanib; hence, there is not an appropriate control group to answer the question "Does mekanib delay vemurafenib resistance?" In other words, there is no data available to support the claim that the addition of mekanib did in fact decrease vemurafenib resistance. Furthermore, the background states that "resistance to these drugs (vemurafenib and dabrafenib) and tumor progression generally occurs in patients within the first year" and the Results section states that the median PFS was 11.6 months in the mekanib group. The median PFS is a little less than a year; hence, the reader should actually question if mekanib actually provided any benefit at all.

The Results section provides information about median PFS and survival rates at 15 months. The length of the study was sufficient to assess the effects it was designed to assess (**choice A**).

The Results section provides information on adverse effects but does not provide any information on drug-drug interactions (**choice B**). Although a drug interaction could potentially decrease the effectiveness of mekanib, the most likely reason to question the validity of the claim (in the question stem) is because of a lack of an appropriate control group.

The Results section states that "Eight patients in the mekanib group and 15 patients in the dacarbazine group withdrew from the study due to severe side effects." Out of an original 447 patients, only 23 patients withdrew from the study. Hence, the subject attrition rate is low for this study (**choice D**).

By definition, the hazard ratio is a measure of relative risk over time in situations where the researchers are interested not only in the total number of events, but also in the timing of these events. For example, the event of interest may be subject death or it could be a non-fatal event such as readmission or symptom change. The use of a hazard ratio in this particular study is appropriate (**choice E**).

3. In the background section of the abstract, researchers state that the purpose of the study was to determine whether the addition of the allosteric MEK1/MEK2 inhibitor mekanib (KAP071714) to vemurafenib treatment would delay drug resistance as well as improve progression free survival (PFS) and overall survival (OS) in comparison to dacarbazine. Which of the following study design changes could have been made to appropriately evaluate all the specified outcomes?

   (A) Add a vemurafenib-only cohort to the study
   (B) Prescribe all 3 medications to each participant but at different dosage ranges
   (C) Replace the dacarbazine cohort with a vemurafenib-only cohort
   (D) Use a crossover study instead of a randomized clinical trial
   (E) No changes were needed since the study was properly designed to meet the specified outcomes

The correct answer is choice A. You are asked to determine what changes could have been made to the original study design so that the 3 initial study outcomes could be appropriately evaluated. Based on the purpose outlined in the question stem, the 3 outcomes being evaluated are as follows:

1. Decreased vemurafenib resistance when mekanib is added
2. Improved PFS for vemurafenib + mekanib compared to dacarbazine
3. Improved OS for vemurafenib + mekanib compared to dacarbazine

The current study design appropriately evaluates PFS and OS between vemurafenib + mekanib AND dacarbazine because participants were administered either vemurafenib + mekanib OR dacarbazine. However, the only way to assess whether mekanib decreases vemurafenib-resistance is to evaluate this regimen against a vemurafenib-only cohort. Hence, in order to appropriately evaluate all 3 outcomes described in the question stem, there would need to be 3 cohorts:

1. Dacarbazine only
2. Vemurafenib only
3. Vemurafenib + mekanib

If researchers prescribed all 3 medications to each participant but at different dosage ranges (**choice B**), then none of the initial 3 outcomes could have been measured because there is no comparison against either dacarbazine only or vemurafenib only.

If researchers replaced the dacarbazine cohort with a vemurafenib-only cohort (**choice C**), then researchers would be able to assess the "resistance outcome." However, they would not be able to assess the effects of mekanib + vemurafenib against dacarbazine.

In crossover studies, all subjects receive both interventions unless it is a placebo-controlled study (then all participants receive treatment and placebo). If a crossover study design were used with the existing study, then group A (for example) would receive dacarbazine only, and group B would receive vemurafenib + mekanib. Then, at some predetermined point there would be a washout period, and group B would receive dacarbazine only and group A would receive vemurafenib + mekanib. This type of study design (**choice D**) would not be able to assess the "vemurafenib resistance outcome" as outlined above.

Research Abstract 3

Efficacy of Imiquimod in Sustained Lesion Clearance in Actinic Keratosis

Actinic keratosis (AK) is a UV light-induced precancerous lesion of thick, scaly or crusty skin that may progress to invasive squamous cell carcinoma. AK is the most common lesion with malignant potential to arise on the skin. Topical fluorouracil has traditionally been the treatment of choice. However, a number of case reports indicated recently that the topical immune response modifier imiquimod successfully detected and cleared both clinical and subclinical lesions across the entire sun-exposed fields of the face and/or balding scalp for a sustained period of time. The purpose of this study was to evaluate the efficacy of topical imiquimod 5% in the field directed treatment of AK against clinical and subclinical lesions, and to determine patient satisfaction with topical imiquimod in the treatment of AK.

Methods

Twenty seven AK patients (with lesions on the face and/or balding scalp) from 9 dermatology practices in Florida were treated with imiquimod 5% twice weekly at bedtime for a period of 12–18 weeks depending on physician preference. Information from their individual findings are summarized here. Lesions were counted before, during, and 3 months post-treatment. Patients compared the imiquimod 5% regimen with their previous AK therapies (if applicable) in terms of treatment duration and side effect profile.

Results

Nineteen of the 27 patients have previously used 1+ prior AK treatments including 5-flurouracil, diclofenac, and photodynamic therapy. The patients had a median of 12 AK lesions on clinical presentation and a median Lmax (maximum lesion count during treatment) of 22. The Lmax initially increased in all patients once treatment stated since imiquimod unmasked previously invisible lesions. The median lesion count was zero 3 months after treatment was completed. At 6 and 12 months of follow-up, the median absolute reduction in AK lesions from Lmax with imiquimod 5% was 20 and 18, respectively. The median percentage reduction in lesions from Lmax to 6 and 12 months was 91% and 82%, respectively. All patients (when asked by the physician) indicated that imiquimod 5% was easy-to-use and that the duration of treatment was better than that of previous AK therapies. Nineteen of the patients considered the side-effect profile of this drug more favorable than that of their prior AK treatments (if applicable).

Conclusion

Imiquimod 5% dosed twice weekly for 12-18 weeks is able to successfully detect and eliminate both clinical and subclinical lesions across the entire sun-exposed fields of the face and balding scalp for sustained long-term efficacy. Imiquimod had a higher patient satisfaction rating than fluorouracil. Imiquimod 5% is thus recommended as a first-line treatment for patients with AK.

Practice Questions

1. Information from the abstract most strongly supports which of the following conclusions about the use of imiquimod in actinic keratosis (AK)?

   (A) Imiquimod had a higher patient satisfaction rating than fluorouracil.
   (B) Imiquimod is a first-line treatment for patients with AK.
   (C) Imiquimod is effective at detecting subclinical AK lesions.
   (D) Imiquimod is equally as effective as topical fluorouracil in the treatment of AK.
   (E) Imiquimod is more effective in the treatment of AK than topical fluorouracil.

The correct answer is choice C. Choice C is most supported by the information provided in the drug abstract. The statement, "Imiquimod is effective at detecting subclinical AK lesions" is supported by the data provided in the Introduction and Results section of the abstract. We are told that "a number of case reports indicated that the topical immune response modifier imiquimod successfully detected and cleared both clinical and subclinical lesions across the entire sun-exposed fields of the face and/or balding scalp for a sustained period of time." The Results section states that "The Lmax initially increased in all patients once treatment stated since imiquimod unmasked previously invisible lesions."

This abstract provides information based on individual case reports. **Choices A, D**, and **E** would generally be the findings of a randomized controlled clinical trial (RCT) where subjects are randomly allocated into "intervention" and "control" groups to receive or not receive an experimental procedure/intervention. RCTs are generally regarded as the most scientifically rigorous studies available in epidemiology.

Choice B may be a true statement, but the information presented in the abstract is based off of the findings of 27 individual case reports. Further study would be needed to justify this statement being true.

2. With respect to the development of invasive squamous cell carcinoma, the use of imiquimod in actinic keratosis (AK) patients as described in this abstract is considered to be what type of prevention?

   (A) Primary prevention
   (B) Secondary prevention
   (C) Tertiary prevention
   (D) Quaternary prevention
   (E) This is a form of curative treatment for squamous cell carcinoma.

The correct answer is A. Disease prevention and health promotion can take different forms. Health professionals and community officials often approach prevention in different ways, so the needs of each person as well as the general population are met. There are different types of prevention activities that can be considered when working with individual patients or with an entire community. It is important that both clinicians and community lead understanding the target population and what type of prevention are necessary to impact people at all levels.

Primary prevention employs the use of preventative measures so that a person does not contract the disease. Primary prevention will decrease both the incidence and prevalence of the disease. In this case, the disease is invasive squamous cell carcinoma. AK is a UV light-induced precancerous lesion of the skin that may progress to invasive squamous cell carcinoma. Preventative measures, such as treatment of a precancerous (AK) lesions, can be employed to prevent the onset of this

condition. Thus, by definition, imiquimod is classified as a primary preventative measure for invasive squamous cell carcinoma.

Secondary prevention (**choice B**) is a form of prevention that is used after the disease has occurred but before the person notices that anything is wrong. Screening for invasive squamous cell carcinoma in high risk individuals is an example of secondary prevention.

According to the CDC, tertiary prevention (**choice C**) targets the person who already has symptoms of the disease. The goals of tertiary prevention are to: (a) prevent damage and pain from the disease, (b) slow down progression of the disease, (c) prevent the disease from causing other complications, (d) give better care to patients with the given disease, and (e) increase the quality of life for a patient with the disease.

Quaternary prevention (**choice D**) is the use of methods to mitigate or avoid consequences of unnecessary or excessive interventions in the health system; the classic example is mitigating the use of antibiotics in children with viral illness.

In this abstract, imiquimod would be a curative treatment measure (**choice E**) for AK and a primary preventative measure for invasive squamous cell carcinoma.

3. Which of the following best describes the type of study performed in this abstract?

   (A) Case-control study
   (B) Case series report
   (C) Crossover study
   (D) Meta-analysis
   (E) Randomized, controlled clinical trial

The correct answer is choice B. The researchers reviewed individual case reports from 9 dermatology practices in Florida. After reviewing and compiling the data from these cases, the authors of the abstract compiled the data from each of the case reports and "Information from their individual findings are summarized here" in this abstract. Based on this information, the information presented in the abstract was most likely derived from a case series report.

A case series report is a type of study that tracks subjects with a known exposure, such as patients who have received a similar treatment (imiquimod), or examines their medical records for exposure and outcome. Case series reports are objective reports of a clinical characteristic or outcome from a group of clinical subjects. For example, patients from 9 dermatology practices diagnosed with actinic keratosis and treated with imiquimod. In a case series report, there is no control group.

Case-control studies (**choice A**) are retrospective observational studies used to identify risk factors that are believed to be associated with a particular disease or condition. Subjects are initially classified as having or not having the disease in question, and then their histories are explored to identify the presence or absence of any risk factors. Data are usually analyzed by means of an odds-ratio and interpreted such that if something occurs in the history of the diseased group, but not in the non-diseased group, then it will be identified as a risk factor.

Crossover studies (**choice C**) are clinical trials in which 2 comparison groups (for example) both receive the drug being tested and the comparative intervention (often a placebo) at different times. This interventional study will generally begin with one group (group A) receiving the investigational drug while a comparison group (group B) receives a placebo. Then, at some predetermined time, there will be a washout period and then group A is

switched to the placebo while group B is given the investigational drug. This study design allows comparison of those on and off the drug, but also satisfies the ethical requirement that everyone in the study is exposed to whatever benefit the experimental drug may provide.

A meta-analysis (**choice D**) will meticulously examine several interventional clinical studies on a particular disease state (or treatment measure) and then combine the results using an acceptable statistical methodology. The results will be presented as if they were from 1 large study. The classical meta-analysis compares 2 types of treatment measures while multiple treatment meta-analysis (or network meta-analysis) can provide estimates of treatment efficacy of multiple treatment regimens, even when direct comparisons are unavailable. A meta-analysis a compilation of interventional studies while a case series report is a compilation of case reports.

In a randomized, controlled clinical trial (**choice E**), a researcher will administer a treatment measure to one group of participants and evaluate its effects against a control group who receives another treatment measure or placebo. Subjects are randomly allocated into "intervention" and "control" groups to receive or not receive an experimental procedure/intervention. In the "imiquimod" abstract, researchers compiled the results from several case reports and evaluated. In this study, patients were NOT originally assigned to receive either imiquimod or another treatment measure, such as fluorouracil.

4. The next step in following up the results presented in this abstract would be to conduct which type of study?

   (A) Case-control study
   (B) Cohort study
   (C) Cross-sectional study
   (D) Randomized, controlled clinical trial
   (E) Replication in a different biological model

The correct answer is D. In the current study, researchers reviewed and compiled the data from numerous case reports. They then attempted to draw causal conclusions from these individual case reports where the treatment was not originally randomly assigned. Using this approach, researchers are able to determine if further investigation is warranted. In this particular analysis, imiquimod successfully detected and eliminated both clinical and subclinical actinic keratosis lesions across the entire sun-exposed fields of the face and balding scalp for sustained long-term efficacy. Based on these results, the next step would be to further validate these findings with an interventional study, such as a prospective, randomized controlled trial (RCT). In an RCT, researchers will randomly assign patients to receive either imiquimod or some other existing treatment measure (such as fluorouracil). Researchers will then be able to determine if there is a statistical difference between the 2 treatment options.

Case-control studies (**choice A**) are retrospective observational studies used to identify risk factors that are believed to be associated with a particular disease or condition. Subjects are initially classified as having or not having the disease in question and then their histories are explored to identify the presence or absence of any risk factors. This type of study would not be an appropriate next step in research.

Cohort studies (**choice B**) are observational studies in which subjects are classified as having or not having a risk factor and then followed forward in time so incidence rates for the 2 groups can be compared. Although cohort studies are a type of prospective study, the next step would be to use an "interventional" prospective study (to determine the efficacy of imiquimod over fluorouracil), such as a randomized controlled clinical trial.

Cross sectional studies (**choice C**) are observational studies used to assess the prevalence of a disease in a given population and what factors co-occur with this disease at a particular time.

Replication in a different model (**choice E**) is generally used in early animal testing of experimental medications. For example, early animal testing for a new compound may involve a small number of rats. Once data is obtained from a single animal test, a lot of information still needs to be obtained before the new compound (experimental drug) could be considered for human trials. Therefore, researchers perform several types of animal testing using a variety of rat species and then other animal models.

5. Which of the following raises the most concern about the validity of the study results?

   (A) Expectancy bias
   (B) Late-look bias
   (C) Measurement bias
   (D) Proficiency bias
   (E) Recall bias
   (F) Selection bias

The correct answer is F. First determine the type of study here and then identify what bias is likely going to affect the reported results. This study would be best classified as a case series report. A case series report is a type of study that tracks subjects with a known exposure, such as patients who have received a similar treatment (imiquimod), or examines their medical records for exposure and outcome. Case series reports are objective reports of a clinical characteristic or outcome from a group of clinical subjects.

Case series reports are particularly susceptible to selection bias (sample selected is not representative of the general population). Examples of case series reports include those that report on a number of patients with a certain illness and/or a treatment of an illness with a single agent. Since case series reports are based on a limited number of individual case reports, they may not appropriately represent the wider population. Internal validity of case series studies is usually very low, due to the lack of a comparator group exposed to the same array of intervening variables.

Expectancy bias (**choice A**) exists when a researcher knows which subjects are in a treatment or a placebo group; this knowledge may cause the researcher, unwittingly, to interact with subjects differently. For example, if the researcher thinks a subject is receiving a better treatment, he is more likely to think the subject is getting better and may perceive effects over and above the physiologic effects of the drugs administered. The way to avoid expectancy bias is a double-blind design, where neither subjects nor the researchers know where each subject is placed. This is not the case here because the "visible" lesions are either present or absent.

Late-look bias (**choice B**) is a problem when gathering information about some types of severe diseases. The problem is that the most severe cases will die or become inaccessible before their information can be gathered. This is not the answer here because AK is a pre-malignant condition and mortality is not an issue.

With measurement bias (**choice C**), something about how the information is gathered affects the information collected. This can occur because survey questions use inappropriate wording that slants respondents to a particular answer, or because just knowing that they are being measured causes people to act differently than they would if they were not observed. The classic example of measurement bias is the Hawthorne effect, where a subjects' behavior is altered simply because they are being studied.

Proficiency bias (**choice D**) is an issue when comparing the effects of different treatments administered at multiple sites. Simply stated, the physicians at one site may have more skill with a given procedure than other physicians do. This means that the different skill level of the physicians delivering treatment might affect patient outcomes more than the treatment selection itself. This was not a comparative study, and only one drug (imiquimod) was administered.

Recall bias (**choice E**) is a problem in retrospective studies, such as a case-control study, where people are asked to remember what happened in the past and report it in the present. If people do not remember and say so, then there is missing data. But often, people will invent answers, either from a desire to please the researcher or because the memory of the past changes over time. In this case, the AK lesions are document by the physician and not "recalled" by the patient.

Type of Bias in Research and Important Associations

Type of Bias	Definition	Important Associations	Solutions
Selection	Sample not representative	Berkson's bias, nonrespondent bias	Random, independent sample
Measurement	Gathering the information distorts it	Hawthorne effect	Control group/placebo group
Experimenter expectancy	Researcher's beliefs affect outcome	Pygmalion effect	Double-blind design
Lead-time	Early detection confused with increased survival	Benefits of screening	Measure "back-end" survival
Recall	Subjects cannot remember accurately	Retrospective studies	Multiple sources to confirm information
Late-look	Severely diseased individuals are not uncovered	Early mortality	Stratify by severity
Confounding	Unanticipated factors obscure results	Hidden factors affect results	Multiple studies, good research design
Design	Parts of study do not fit together	Non-comparable control group	Random assignment

Pharmaceutical Ad 1

Tazofect

(tanzopanib 10 and 20 mg capsules)

For newly diagnosed and treatment-resistant EGFR-mutated NSCLC, an effective treatment is now available to improve progression-free survival (PFS)!

- Tazofect is indicated for treatment of EGFR-mutated NSCLC
- Tazofect has shown efficacy in PIK3CA, PTEN, and KRAS-mutated NSCLC

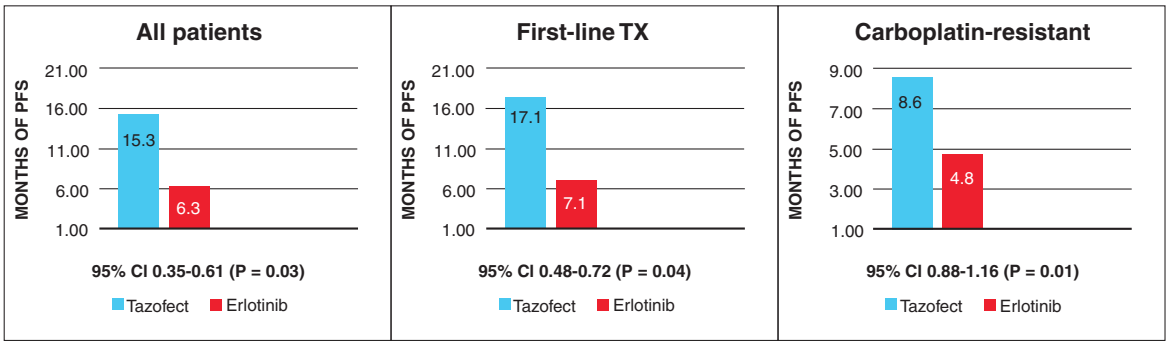
Tazofect is like extra time in a capsule...

...so your patients have more time to do what they want to do!

Tazofect has been proven to:

- Increase PFS by an average of 9 months in all NSCLC study participants (first-line and erlotinib resistant)
- Increase PFS by an average of 10 months in first line NSCLC study participants over those receiving Tarceva® (erlotinib)
- Almost double the PFS in carboplatin resistant NSCLC study participants over those receiving Tarceva® (erlotinib)

The side effect profiles for both Tazofect and erlotinib were similar.



- The effects of Tazofect (10-20 mg qd) and erlotinib (150-200 mg qd) in subjects with EGFR exon 19 deletions or exon 21 (L858R) substitution mutations are presented above. The results were taken from a phase 3, randomized, double blinded multicenter clinical trial. Per protocol, each of these agents was continued until clinically significant disease progression occurred plus an additional 2 months unless mortality occurred. The average follow-up time for patients who completed the study in both Tazofect groups was 17.3 months and 8.3 months in both erlotinib groups.
- Of the 800 initial participants enrolled in the phase 3, randomized, double blinded multicenter trial, 225 (of 398) participants completed the study in the Tazofect group and 388 (of 402) participants completed the study in the erlotinib group.
- Of the original number of study participants, 103 Tazofect patients and 102 erlotinib patients were classified as carboplatin-resistant.

Increased progression-free survival!

Additional product information provided below

SMILE Pharmaceuticals

Smile for life with SMILE Pharmaceuticals

Improved patient outcomes!

HIGHLIGHTS OF PRESCRIBING INFORMATION

Please see Tazofect (tanzopanib) drug package insert for complete prescribing information

Indications and Usage: Tazofect (tanzopanib) is a kinase inhibitor indicated for first-line treatment of NSCLC with EGFR exon 19 deletions and EGFR exon 21 (L858R) substitution mutations in patients age 18 years and older.

Mechanism of Action: Tanzopanib is a kinase inhibitor that acts by inhibiting intracellular tyrosine kinase domain of epidermal growth factor receptor (EGFR) thus resulting in cell cycle arrest and angiogenesis inhibition. Tanzopanib has an elimination half-life of approximately 28 hours in patients with normal hepatic and renal function.

Dosage and Administration: Treatment of NSCLC with EGFR exon 19 deletions and EGFR exon 21 (L858R) substitution mutations in patients aged 18 years and older with normal hepatic and renal function: 10-20 mg daily until clinically significant disease progression.

Contraindications: Hypersensitivity to tanzopanib; use in patients with severe hepatic impairment, active infection and thrombocytopenia.

Warnings and Precautions: May cause reactivation of tuberculosis and hepatitis B. Use caution in patients receiving other chemotherapeutic agents, thyroid disorders, dehydration, mild to moderate renal and hepatic dysfunction

Adverse Reactions:

Common (≥5%): elevated AST & ALT (15%), diarrhea (15%), fatigue (13%), elevated bilirubin (12%), infection (10%), cough (8%), thrombocytopenia (7%)

Less common (<5%): hepatorenal syndrome (2%), hepatotoxicity (2%), toxic epidermal necrolysis (1%), Stevens-Johnson syndrome (1%), acute renal failure (1%), hypothyroidism (1%), hemolytic anemia (<1%)

Practice Questions

1. The data provided in the drug advertisement most strongly supports which of the following conclusions?

   (A) In the treatment of cancer, Tazofect and erlotinib can be used interchangeably.

   (B) Tazofect is not indicated for treatment of EGFR exon 19 insertion in non-small cell lung cancer.

   (C) Tazofect should be considered for use in patients with PIK3CA mutated NSCLC.

   (D) The combination of Tazofect and erlotinib will improve the PFS to a greater extent than either agent alone.

   (E) The dose of Tazofect should be adjusted in patients with hepatic dysfunction.

The correct answer is B. The key to answering this type of question is to first rapidly scan the drug ad and highlights of prescribing information so that you are able to obtain a general sense of how the content is arranged. Then read the question and quickly search for each of the answer choices in the body of the drug ad itself. In the Indications section of the prescribing information, the following is stated. "Tazofect (tanzopanib) is a kinase inhibitor indicated for first-line treatment of NSCLC with EGFR exon 19 deletions and EGFR exon 21 (L858R) substitution mutations in patients aged 18 years and older." There is no mention of "EGFR exon 19 insertions." That is not to say that the drug cannot be used in NSCLC patients with EGFR exon 19 insertions. However, Tazofect is not indicated (FDA approved) for use in these patients by the FDA. Hence this is a true statement and the correct answer.

Both Tazofect and erlotinib are indicated for EGFR exon 19 deletions or exon 21 (L858R) substitution mutations. Also both drugs are noted to have similar side effect profiles (as indicated in the primary drug ad). However, erlotinib is also indicated for the treatment of pancreatic cancer. Since erlotinib has a broader range of clinical indications and choice A states "in the treatment of cancer," these agents are not interchangeable. It should also be pointed out that almost half of the Tazofect patients dropped out of the trial. Without knowing the reasons why, it would not be advisable to interchange Tazofect with erlotinib. Choice A is a false statement.

Choice C states that "Tazofect should be considered for use in patients with PIK3CA mutated NSCLC." Although the main drug ad states that "Tazofect has shown efficacy in PIK3CA, PTEN and KRAS Mutated NSCLC," there is no data in the prescribing information or drug ad itself to support this claim. Also what exactly does "shown efficacy" mean? The drug may be marginally effective in a small percentage of PIK3CA patients, for example. In other words, there is no data to support this claim in the drug ad. Choice C is an incorrect statement.

Choice D states that "The combination of Tazofect and erlotinib will improve the PFS to a greater extent than either agent alone." There is no information indicating whether the combination of the 2 agents will provide more benefit, less benefit, or the same benefit as either agent used alone. Choice D is an incorrect statement.

Choice E refers to making a dosing adjustment in patients with hepatic dysfunction. In the prescribing information section, there is a contraindication for use in severe hepatic impairment as well as a precaution about use in patients with mild-moderate hepatic dysfunction. However, there is no information provided in the drug ad related to a dosing adjustment in patients with hepatic dysfunction. Choice E is an incorrect statement.

2. Consider the following statement: "Tazofect was proven to provide approximately double the PFS in carboplatin resistant NSCLC study participants over those receiving Tarceva® (erlotinib)." When evaluating the drug ad and highlights of prescribing information, which of the following provides the best evidence that this statement is inaccurate?

   (A) Number of patients treated in the carboplatin resistant group for both drugs
   (B) The calculation of months of PFS for the carboplatin resistant graph
   (C) The confidence interval for the carboplatin resistant graph
   (D) The *p*-value for the carboplatin resistant graph
   (E) The *y*-axis data points for the carboplatin resistant graph

The correct answer is C. You are asked to evaluate a statement found on the main drug ad and then indicate what information provided in the drug ad invalidates this statement. Of all the answer choices, the data provided on the confidence interval for the carboplatin resistant graph provides the best evidence that the statement is inaccurate. A confidence interval gives an estimated range of values that is likely to include an unknown parameter (such as actual PFS), the estimated range being calculated from a given set of sample data. In the original statement, the drug company claimed that their drug (Tazofect) was proven to provide approximately double the PFS in carboplatin resistant NSCLC study participants over those receiving Tarceva® (erlotinib). However, the confidence interval provided with the carboplatin resistant graph contains the number 1. If the 95% confidence interval for a study includes 1.0, then there is >1 in 20 chance that random variation in outcome incidence among the study groups (Tazofect-study and erlotinib-control) is what produced the observed correlation between treatment and outcome. In this instance the *p*-value is also likely to be >0.05. In summary, if the confidence interval contains the relative risk of 1.00, the result is not significant. As discussed, this should also lead the reader to believe that the *p*-value (provided on the same graph, choice D) is also inaccurate. However, without the data seen with the confidence interval, the reader would have no way of suspecting that the provided *p*-value is also likely inaccurate. Therefore, choice C is the best answer

In the key under the 3 graphs, it is stated that 103 Tazofect patients and 102 erlotinib patients were classified as carboplatin resistant. This is a sufficient number of patients in each group (**choice A**).

The statement makes reference to the number of months of PFS in the Tazofect group being "almost double" the erlotinib group in carboplatin resistant patients. The PFS for Tazofect is 8.6 months and the PFS for erlotinib is 4.8 months. This statement could have been phrased differently, but is not completely inaccurate (**choice B**).

When comparing the data points on the *y*-axes of the 3 graphs, the *y*-axis on the carboplatin resistant group was clearly manipulated so that a more "profound graphical representation" of the actual results is evident. Although this should cause the reader to question the integrity of the authors, choice C is still the best answer.

3. Shortly after Tazofect is released for use in the general population, the FDA and drug manufacturer begin to receive numerous reports of complete treatment failure in both carboplatin resistant patients and first-line therapy patients as well as higher than expected percentages of adverse events in all patients. Which of the following is the most likely reason for these reports on Tazofect?

   (A) Insufficient follow-up of study participants
   (B) Insufficient information on adverse effects
   (C) Insufficient information on drug indications
   (D) Subject attrition
   (E) Type II error was committed

The correct answer is choice D. In the question stem we are told that shortly after the drug is used in the general population there are reports of treatment failure in both carboplatin resistant patients and first-lines treatment patients. We are also told that higher-than-expected percentages of adverse events are occurring. The question is asking for the most likely cause of this occurrence. The most likely reason based on the data provided in the drug ad and highlights of prescribing information is subject attrition. Under the 3 graphs it is stated that "Of the 800 initial participants enrolled in the phase 3, randomized, double blinded multicenter trial, 225 (of 398) participants completed the study in the Tazofect group and 388 (of 402) participants completed the study in the erlotinib group." Approximately half (225/398 participants) of the original Tazofect study participants never completed the trial. Furthermore, the authors did not provide an explanation as to why they did not complete the study. Is it likely that they did not complete the trial because of severe adverse effects and/or death?

Without knowing the reasons why the participants never completed the trial, it is difficult to evaluate the safety and efficacy of Tazofect in both first-line therapy and carboplatin resistant patients. Also, it is quite possible that only a small percentage of the 103 participants in the carboplatin resistant arm of the study never completed the study. Without more information, it is hard for the reader to make a valid conclusion. In summary, the authors should have indicated why almost half of the study participants never completed the study; hence, the primary reason why these reports are occurring (due to treatment failures and increased adverse effect occurrence) is directly related to the circumstances surrounding the high level of subject attrition in this trial.

The phase 3 trial for Tazofect lasted in each patient until clinically significant disease progression occurred, plus an additional 2 months unless mortality occurred. Furthermore, the average follow-up time for patients who completed the study was listed. The length of the study was sufficient to assess the effects it was designed to assess. Choice A is an incorrect response.

At the bottom of the highlights of the prescribing information page of the drug ad, there is an extensive list of adverse effects and percentage of occurrence of each of these side effects. Hence, sufficient information on these adverse effects was provided. Choice B is an incorrect response. However, this information was based on the number of patients who completed the clinical trial. Since almost half of the study participants (in the Tazofect arm) never completed the trial, an accurate accounting of side effect appearance was not available. This is directly related to subject attrition.

At the top of the highlights of prescribing information page of the drug ad, it clearly states that "Tazofect (tanzopanib) is a kinase inhibitor indicated for first-line treatment of NSCLC with EGFR exon 19 deletions and EGFR exon 21 (L858R) substitution mutations in patients aged 18 years and older." The drug is NOT indicated for use in carboplatin resistant patients. Although there is a graph on the first page of the drug ad and comments about proven effects, the drug ad never claimed that the drug was "indicated" for use in carboplatin patients. Choice C is an incorrect response.

A type II or beta error is where the researcher fails to reject the null hypothesis when it is really false. In other words, the researcher declared that there was no significant effect on the basis of the sample when there really is one in the population. The likely impact of this type of error is that the drug (Tazofect) would NOT obtain FDA approval, and the general population would not receive this medication. Choice E is an incorrect response.

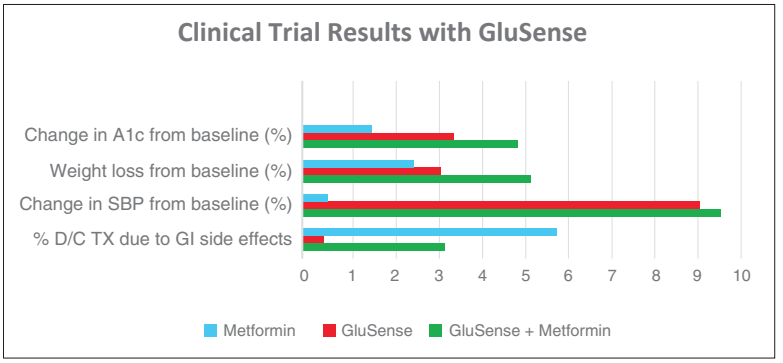
Pharmaceutical Ad 2

GluSense™ ... because it makes sense!

(Glugliflozin 75 mg, 150 mg and 300 mg tablets)

Diabetes is a complex disease ...

GluSense is a simple treatment measure with proven therapeutic outcomes!



- The clinical effects of GluSense (150-mg qd), metformin (1000 mg bid), and combination therapy (GluSense 150 mg qd + metformin 1000 mg bid) in patients with newly diagnosed type 2 diabetes who failed to meet glycemic goals with diet and exercise alone are presented above. The results were taken from a phase 3, randomized, double-blinded multicenter clinical trial.
- Each therapy was administered in conjunction with a structured diet and exercise program.
- A baseline A1c, body weight, and systolic blood pressure reading were obtained at the onset of the trial and every 8 weeks during the trial. All participants were enrolled in the study for 12 months.
- Of the 2000 initial participants enrolled in the trial, 462 (of 510) participants in the metformin-only group completed the study, 358 (of 533) of the GluSense-only group completed the study, and 313 (of 577) in the GluSense + metformin group completed the study. Thirty-eight of the 380 participants in the control group withdrew.
- The primary reason (as stated by the patient) for withdrawing from the study was unwanted side effects.

GluSense demonstrated greater reductions in A1c, weight loss & blood pressure than metformin alone at 52 weeks!

- GluSense is indicated for treatment of T2DM as monotherapy & in combination with metformin.
- GluSense has shown efficacy when used in conjunction with other oral hypoglycemic agents.

The treatment your T2DM patients have always needed is finally here!!

SMILE Pharmaceuticals

Smile for life with SMILE Pharmaceuticals

GluSense has been proven to:

- Reduce A1c in T2DM patients by an average of 3.4% as monotherapy ($p<0.001$) & in combination with metformin an average of 4.9% ($p<0.002$) – mean baseline A1c = 8.05%
- Reduce baseline weight in T2DM patients by an average of 3.1% as monotherapy ($p<0.02$) & in combination with metformin an average of 5.2% ($p<0.03$) – mean baseline weight = 182 lb (87.3 kg)
- Reduce baseline systolic blood pressure in T2DM patients by an average of 9.1% as monotherapy ($p<0.006$) & in combination with metformin an average of 9.6% ($p<0.001$) – mean baseline SBP = 177 mm Hg.

Additional product information provided below

HIGHLIGHTS OF PRESCRIBING INFORMATION

Please see GluSense (glugliflozin) drug package insert for complete prescribing information.

Indications and Usage: GluSense (glugliflozin) is indicated for the treatment of type 2 diabetes in conjunction with diet and exercise as monotherapy, and in combination with metformin in patients aged 18 years and older.

Mechanism of Action: Glugliflozin is an SGLT2 inhibitor with insulin-sensitizing properties. This agent has a dual mechanism of action. It acts by:

Inhibiting the sodium-glucose cotransporter 2 (SGLT2), thereby reducing glucose reabsorption and increasing urinary glucose excretion

Decreasing insulin in the periphery and liver, resulting in increased insulin-dependent glucose disposal and decreased hepatic glucose output. Glugliflozin is an agonist for peroxisome proliferator-activated receptor-gamma (PPARγ). Activation of PPARγ nuclear receptors in the liver, skeletal muscle, and adipose tissue modulates the transcription of a number of insulin responsive genes involved in the control of glucose and lipid metabolism.

Other: antagonizes peripheral alpha-1 adrenergic receptors

Pharmacokinetics

Glugliflozin has an elimination half-life of approximately 16 hours in patients with normal hepatic and renal function.

Following oral administration of glugliflozin, Tmax occurs within 3 hours.

Glugliflozin is extensively metabolized by hydroxylation and oxidation; the metabolites also partly convert to glucuronide or sulfate conjugates.

Following oral administration of glugliflozin, approximately 15–20% of the drug dose is recovered in the urine.

Dosage and Administration: Treatment of type 2 diabetes in patients aged 18 years or older who have failed to meet glycemic goals with diet and exercise alone:

Monotherapy: 150-300 mg PO qd; start at 75 mg PO qd and increase by 75 mg qwk; max dose 450 mg/day

Combination with metformin: same as monotherapy and standard metformin dose of 2000 mg daily (in divided doses)

Contraindications: Type 1 diabetes mellitus, hypersensitivity to glugliflozin and/or sulfonamides; NYHA class III or IV heart failure, severe hepatic impairment, hyperkalemia, use with medications causing hyperkalemia and diabetic ketoacidosis

Warnings and Precautions: May cause hypoglycemia, hypotension, and AST/ALT elevation. Caution use in elderly patients with poorly controlled diabetes and patients with past history of cardiovascular disease.

Adverse Reactions (for a complete list, see drug package insert)

Common (≥5%):	Less Common (<5%):
Hyperkalemia	Fatigue
Hypoglycemia	Hepatic dysfunction
Orthostatic hypotension	Thirst
Dizziness	Fainting
Tachycardia	Mental impairment
Hyperhidrosis	Pancreatitis

Drug Interactions (see drug package insert)

Practice Questions

1. The data provided in the drug advertisement most strongly supports which of the following conclusions?

   (A) GluSense is a substitute for diet and exercise in type 2 diabetes due to its weight loss properties.

   (B) GluSense is recommended for use in patients with a history of myocardial infarction.

   (C) GluSense is safer to use in patients with type 2 diabetes than metformin.

   (D) The antihypertensive effects of GluSense are comparable to some currently available antihypertensive medications.

   (E) The combination use of GluSense and a sulfonylurea is recommended for those who initially fail sulfonylurea monotherapy.

The correct answer is D. This type of question generally requires a process of elimination. The statement "The antihypertensive effects of GluSense are comparable to some currently available antihypertensive medications" is most strongly supported by the drug ad. Relevant information to support this statement can be found in several places: First in the table, GluSense is associated with 9.1% decrease in average systolic blood pressure. This percentage decrease is comparable to the diuretics, low-moderate doses of ACE inhibitors, alpha antagonists, as well as varying doses of other drugs from different drug classes. Second, the mechanism of action section of the highlights of prescribing information states that this drug antagonizes peripheral alpha-1 adrenergic receptors. This is the same mechanism of action as drugs like terazosin and doxazosin. Finally, the side effects of the drug (orthostatic hypotension, dizziness, and tachycardia) also support its antihypertensive properties since these are side effects commonly seen in alpha antagonists. Hence, out of all of the answer choices, this statement is most strongly supported by the drug ad.

There are several places which indicate GluSense is used in conjunction with diet and exercise, such as the key under the chart on the main ad page and in the Indications and Usage section in the highlights of prescribing information. Although the drug promotes weight loss, GluSense is not a substitute for diet and exercise (**choice A**).

The Warnings and Precautions section states that GluSense should be used cautiously in patients with past history of cardiovascular disease. Furthermore, in Contraindications, it is stated that GluSense is contraindicated for use in patients with NYHA Class III or IV heart failure. Since myocardial infarction (**choice B**) is a form of cardiovascular disease and a common precipitating cause of heart failure, GluSense would not be recommended for use in these cases. GluSense may potentially be used "cautiously" in patients with a mild form of cardiovascular disease but is not "recommended."

The drug ad does not have a safety profile comparison between GluSense and metformin (**choice C**). The only related comparison between the drugs is the appearance of severe GI side effects leading to withdrawal from the study.

The only statement relating to the use of GluSense and another drug is found in the main area of the drug ad: "GluSense has shown efficacy when used in conjunction with other oral hypoglycemic agents." It does not specify the names or drug classes of the other agents (**choice E**). Furthermore, it does not provide any data to support this claim.

2. Of the initial trial participants, 175 persons from the GluSense-only group and an even large number from the GluSense and metformin group withdrew from the study. Which of the following is the most likely reason for participant withdrawal?

   (A) Appearance of drug interactions
   (B) Hypersensitivity to sulfonamides
   (C) Severe hypoglycemia
   (D) Severe hypotension
   (E) Severe GI side effects

The correct answer is C. You are asked to determine the most likely reason why participants withdrew from the study. In the key under the graph on page 1, it states "The primary reason (as stated by the patient) for withdrawing from the study was unwanted side effects." However, it is not stated what side effect caused them to withdraw. Therefore, you must determine the most likely reason based on information provided in the drug ad. The Adverse Reactions section of the highlights of prescribing information provides only a "partial" list of side effects with a percent occurrence above and below 5%, so this section alone cannot be used to answer the question. The correct answer can be derived from the section on the bottom right of the main drug ad. It states that GluSense has been proven to reduce A1c in type 2 diabetes (T2DM) patients by an average of 3.4% as monotherapy ($p<0.001$) and in combination with metformin an average of 4.9% ($p<0.002$). The mean baseline A1c was 8.05% for study participants. An average change would affect the median, so we would expect study A1c post-treatment to be 4.65% and 3.15%, respectively. Since these are at or below the bottom of the expected normal range, we would expect a significant number of patients to be hypoglycemic. That is proportionally a greater effect than what would be seen with systolic blood pressure (SBP). Note that the graph is ambiguous as to whether changes noted are relative percent changes or absolute percent changes. For non-percent values (SBP and weight loss), these must be relative changes (10% decrease in an SBP of 100 mm Hg would mean SBP 90 mm Hg). For percent values (A1c and withdrawal from study), these are more likely to be absolute changes since a relative decrease of 1.5% for metformin would be insignificant and an absolute decrease is more in line with what is expected. Choice C is the best answer choice.

The drug ad does not specifically mention any problems with drug-drug interactions (**choice A**) in the clinical trial and there is a comment indicating that the reader should please see GluSense (glugliflozin) drug package insert for complete prescribing information. Based on this information, it is unlikely that drug-drug interactions are the primary reason for patient withdrawal.

The Contraindications section states that GluSense is contraindicated for use in patients with sulfonamide hypersensitivity (**choice B**). However, there is nothing which would lead the reader to believe this is the primary reason for withdrawal from the study.

The bottom right of the ad states that GluSense has been proven to reduce baseline SBP in T2DM patients by an average of 9.1% as monotherapy ($p<0.006$) and in combination with metformin an average of 9.6% ($p<0.001$). The mean participant baseline SBP was 177 mm Hg. Even if the starting blood pressure was 100 mm Hg, the patient would still not be hypotensive with a 9.6% drop in blood pressure. Note, too that orthostatic hypotension is listed as a common side effect, but with the information presented it is unlikely that was the primary reason for patient withdrawal (**choice D**).

It is unlikely that severe GI side effects (**choice E**) were the primary reason for participant withdrawal since the table shows that the GluSense-alone arm had almost no withdrawals from study. GluSense also improved the GI side effect withdrawal rate for patients receiving metformin when the 2 medications were combined.

3. A 64-year-old man comes to the physician with complaints of increasing polyuria and polydipsia. His past medical history is significant for type 2 diabetes, hypertension, hyperlipidemia, and a myocardial infarction 4 years ago. Allergy history includes an anaphylactic reaction to levofloxacin. He is currently receiving metformin 1000 mg 2x daily, enalapril 10 mg daily, pravastatin 20 mg daily, and spironolactone 25 mg twice daily. Physical examination shows blood pressure of 126/82 mm Hg, heart rate 62/min, height 172.7 cm (5 feet, 8 inches), weight 88.6 kg (195 lb), and BMI 29.6.

   Laboratory studies show:

   - Blood glucose: 215 mg/dL
   - A1c: 10.5%
   - Albumin: 3.8 g/dL
   - Creatinine: 1.3 mg/dL
   - AST: 20 IU/L
   - ALT: 22 IU/L
   - Sodium: 138 mEq/L
   - Potassium: 4.9 mEq/L
   - Calcium: 9.6 mg/dL
   - Ejection fraction: 66%

   If the attending physician is considering the addition of GluSense to this patient's medication regimen, which of the following is a contraindication for prescribing this medication?

   (A) Allergy contraindication
   (B) Cardiovascular contraindication
   (C) Drug interaction contraindication
   (D) Hepatic contraindication
   (E) Renal contraindication
   (F) There is no contraindication in this patient, and the medication can be prescribed.

The correct answer is C. You are being asked for the most likely reason to not prescribe this medication to a given patient. Therefore, you need to look for either an absolute or relative contraindication for prescribing this medication in the drug ad. The Contraindications section states that GluSense is contraindicated for "use with medications causing hyperkalemia." The patient is currently receiving enalapril and spironolactone. Both of these medications are associated with the development of hyperkalemia. Furthermore, the patient's potassium level is 4.9 mEq/L, which is at the high level of normal. The patient is likely to become hyperkalemic once starting this medication. Based on this information, a drug-drug interaction (**choice C**) between GluSense and both enalapril and spironolactone is the most likely contraindication for use of this medication in this patient. Choice C is correct and choice F is incorrect.

The patient has a history of anaphylaxis to the fluoroquinolone levofloxacin. Although GluSense is contraindicated for use in patients with a sulfonamide allergy, there is no allergy contraindication for using this medication in patients with a fluoroquinolone allergy (**choice A**).

The only cardiovascular contraindication (**choice B**) listed for GluSense is NYHA Class III or IV heart failure. This patient has a normal ejection fraction of 66% (normal 55-70%) so does not meet the cardiovascular contraindication criteria for this drug. Although the patient's past history of myocardial infarction predisposes him to heart failure, the patient currently does

not have heart failure so there is no contraindication. However, there is a warning for use of GluSense in patients with cardiovascular disease. As indicated, this patient has a past history of a myocardial infarction as well as hyperlipidemia and hypertension. Therefore, this medication should be used cautiously in this patient. If GluSense is prescribed, the patient should be monitored closely, but there is no cardiovascular contraindication for the use of this drug in this patient.

The patient has normal hepatic function (AST: 20 IU/L (normal <35 IU/L) and ALT 22 IU/L (normal <35 IU/L)); hence, there is no hepatic contraindication for using GluSense in this patient (**choice D**).

The patient has normal renal function (creatinine: 1.3 mg/dL (normal 0.5-1.4 mg/dL)); hence, there is no renal contraindication for using GluSense in this patient (**choice E**).

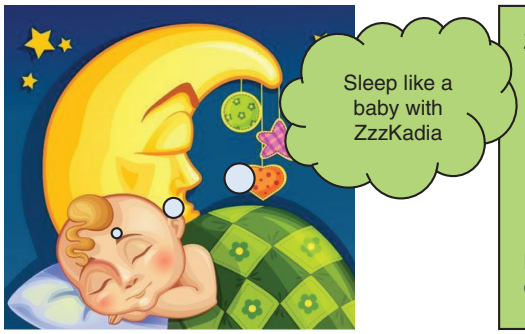
Pharmaceutical Ad 3

Zzzkadia™

(Zlideplon 2.5, 5, 7.5 mg tablets)

The only orexin receptor antagonist with $GABA_BZ$ receptor modulator properties indicated for long-term treatment of insomnia!

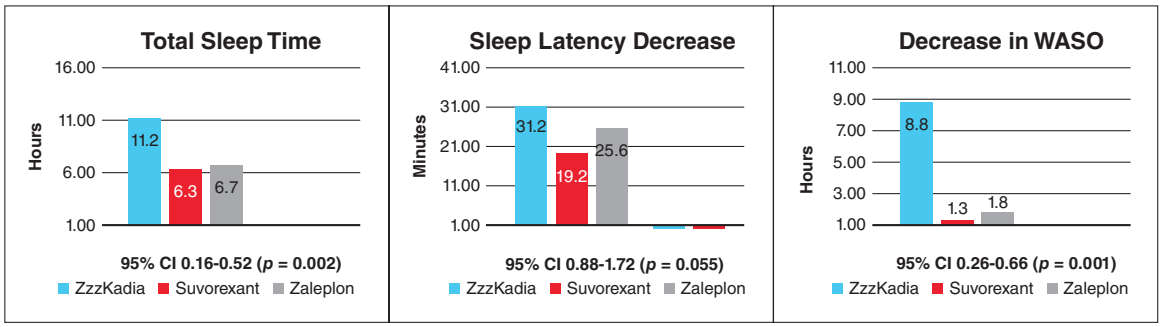
- TIndicated for long-term treatment of insomnia
- Shown to be non-addicting
- The most effective sedative/hypnotic available



ZzzKadia has been proven to:

- Increase mean total sleep times (TST) by 5.7 hours compared to 1.3 hours with suvorexant and 1.1 hours with zaleplon
- Significantly decrease sleep latency (SL) over both suvorexant and zaleplon
- Significantly decrease wake time after sleep onset (WASO) over both suvorexant and zaleplon

Most common side effects: headache, dizziness, lightheadedness, daytime drowsiness, somnolence, and nightmares



- The effects of ZzzKadia (5 mg HS), Suvorexant (10 mg HS) and Zaleplon (5 mg HS) were evaluated in participants age 35-70 with a DSM-5 diagnosis of insomnia disorder who have not previously used prescription sedative/hypnotics. The results were taken from a 16-week phase 3, randomized, double blinded multicenter clinical trial. Per protocol, patients were instructed to take 10 minutes prior to bedtime 5 times per week maximum.
- Of the 651 initial participants enrolled in the study 137 (of 222) ZzzKadia, 198 (of 220) suvorexant and 192 (of 209) zaleplon participants completed the study.
- Following the study, each of the medications was discontinued and 93% of all participants (who completed the trial) requested further treatment due to the reemergence of severe insomnia as well as side effects ranging from autonomic hyperactivity to psychomotor agitation to seizures.

Increased total sleep time!

Additional product information provided below

SMILE Pharmaceuticals

Smile for life with SMILE Pharmaceuticals

Improved daytime function!

HIGHLIGHTS OF PRESCRIBING INFORMATION

Please see ZzzKadia (Zlideplon) drug package insert for complete prescribing information.

Indications and Usage: ZzzKadia (Zlideplon) is an orexin receptor antagonist with $GABA_BZ$ receptor modulator properties indicated for first-line treatment of short-term insomnia and insomnia disorder (according to DSM-5 diagnostic criteria) in patients age 35 years and older.

Mechanism of Action: Zlideplon is an orexin receptor antagonist with $GABA_BZ$ receptor modulator properties. Specifically zildeplon is a selective dual antagonist of orexin receptors OX1R and OX2R that promotes sleep by reducing wakefulness and arousal. It also exerts its action through subunit modulation of the $GABA_BZ$ receptor chloride channel macromolecular complex. Zildeplon also binds to the brain omega-1 receptor located on the alpha subunit of the GABA-A/chloride ion channel receptor complex and potentiates t-butyl-bicyclophosphorothionate (TBPS) binding. Zlideplon has an elimination half-life of approximately 10 hours in patients with normal hepatic function.

Dosage and Administration: Treatment of short-term insomnia and insomnia disorder in patients age 35 years and older with normal hepatic and renal function: 2.5-5 mg PO at bedtime. Maximum dose per day is 7.5 mg.

Contraindications: Hypersensitivity to zlideplon or sulfonylureas; abrupt discontinuation or use in patients with severe hepatic impairment.

Warnings and Precautions: Use caution in the patient who is sensitive to sulfonylureas; has a past history of depression or substance use disorder; drives or operates heavy machinery, or has altered CYP3A4 function (especially CYP3A4 poor metabolizers).

Adverse Reactions:

Common (>5%): orthostatic hypotension (25%), tachycardia (18%), headache (15%), dizziness (13%), lightheadedness (12%), daytime drowsiness (10%), hypotension (9%), somnolence (8%), decreased coordination (7%); memory impairment (5%) and nightmares (5%)

Less common (<5%): hepatotoxicity (2%), toxic epidermal necrolysis (1%), Stevens-Johnson syndrome (1%), diarrhea (1%), paresthesia (1%), and ocular pain (<1%)

Practice Questions

1. The data provided in the drug advertisement most strongly supports which of the following claims?

   (A) The dose of ZzzKadia should be adjusted in patients with hepatic dysfunction.
   (B) Zzzkadia improves daytime function.
   (C) ZzzKadia is indicated for long-term treatment of insomnia.
   (D) ZzzKadia is the most effective sedative/hypnotic.
   (E) ZzzKadia significantly decrease sleep latency (SL) over both suvorexant and zaleplon.

The correct answer is D. Of the 3 medications studied (ZzzKadia, suvorexant, zaleplon), ZzzKadia is significantly more effective than the other 2 agents in terms of total sleep time (TST) and wake time after sleep onset (WASO). These facts are supported by both the confidence intervals and p values provided.

In the prescribing information section, there is a contraindication for use in severe hepatic impairment as well as a precaution about use in patients with altered CYP3A4 function (especially CYP3A4 poor metabolizers). Although a dosage adjustment in patients with renal dysfunction is likely, there is no information provided in the drug ad related to a dosing adjustment in patients with hepatic dysfunction (**choice A**).

The side effects for this drug include headache (15%), dizziness (13%), lightheadedness (12%), daytime drowsiness (10%), somnolence (8%), decreased coordination (7%) and memory impairment (5%). There is no indication that this drug improves daytime function (**choice B**).

In the main drug ad it is stated that "the results were taken from a 16-week phase 3, randomized, double blinded multicenter clinical trial." This timeframe does not constitute long-term efficacy (**choice C**). Furthermore, in the indications section of the prescribing information it is stated that ZzzKadia is indicated for the treatment of short-term insomnia and insomnia disorder (according to DSM-5 diagnostic criteria).

Choice E refers to the stated decrease in sleep latency (SL) over both suvorexant and zaleplon. This statement is false based on the confidence interval provided for SL. If the given confidence interval (for relative risk or odds ratio) contains 1.0 (as seen in the SL graph), then there is no statistically significant effect of exposure. If the confidence interval for an OR does not contain the number "1" then the following rules apply to the odds ratio:

- If OR > 1, the exposure is associated with a higher risk of outcome
- If OR < 1, the exposure is associated with a lower risk of outcome

2. Although not mentioned in the mechanism of action for ZzzKadia, this drug most likely has which of the following pharmacological properties?

   (A) Alpha 1 antagonist
   (B) Beta 1 agonist
   (C) Beta 2 antagonist
   (D) Muscarinic 2 agonist
   (E) Muscarinic 3 antagonist

The correct answer is A. You are being asked to determine the additional pharmacological effects of ZzzKadia, which is currently described as an orexin receptor antagonist with $GABA_BZ$ receptor modulating properties. The best way to answer this question is to review the adverse effects and match several of these effects to the correct answer choice. Since most of the

CNS-related adverse effects are caused by interaction with the orexin and GABA receptors, the focus should be on the non-CNS related effects. The high incidence of orthostatic hypotension (25%), tachycardia (18%), and hypotension (9%) suggests that the drug has some cardiovascular effects. Of the answer choices, only alpha 1 antagonists (such as terazosin) would cause these cardiovascular effects.

Beta 1 agonists (**choice B**) are likely to cause increased heart rate, conduction velocity, and force of contraction leading to hypertension (not hypotension).

Beta 2 antagonists (**choice C**) will block the beta-2 receptors found on blood vessels that are responsible for vessel dilation. Hence, blood pressure will not change or may increase.

Muscarinic 2 receptors are primarily located on the heart and when stimulated lead to decreased heart rate. However a muscarinic 2 receptor antagonist (**choice D**) will block these receptors, leading to tachycardia and increased blood pressure secondary to the unopposed beta 1 receptor effects.

Muscarinic 3 receptors are non-innervated receptors located on blood vessels. Antagonism (**choice E**) of these receptors would cause no change in blood pressure since stimulation (via nitrous oxide endothelium-derived relaxing factor) leads to dilation.

3. Consider the following statement: "ZzzKadia has been shown to be non-addicting!" When evaluating the drug ad and highlights of prescribing information for ZzzKadia, which of the following provides the best evidence that this statement is inaccurate?

   (A) Long drug half-life
   (B) Presence of euphoric symptoms
   (C) Presence of severe side effects
   (D) Presence of withdrawal symptoms
   (E) This is an accurate statement

The correct answer is D. You are being asked why ZzzKadia is likely an addictive substance with abuse potential. The first step is to understand the definition of abuse potential. According to the FDA, abuse potential refers to a "drug that is used in nonmedical situations, repeatedly or even sporadically, for the positive psychoactive effects it produces. These drugs are characterized by their CNS activity. Examples of the psychoactive effects they produced include sedation, euphoria, perceptual and other cognitive distortions, hallucinations, and mood changes. Drugs with abuse potential often (but not always) produce psychic or physical dependence (leading to withdrawal when substance is removed) and may lead to the disorder of addiction."

In the main drug ad, the following is stated: "Following the study, each of the medications was discontinued and 93% of all participants (who completed the trial) requested further treatment due to the reemergence of severe insomnia as well as side effect ranging from autonomic hyperactivity to psychomotor agitation to seizures." Based on this information and the FDA definition of abuse potential, when ZzzKadia is abruptly withdrawn, physical side effects (including CNS effects) are seen.

Half-life and the presence of severe side effects (**choices A and C**) have no established impact on abuse potential.

Euphoric symptoms (**choice B**) are probably the most common reason why prescription and illicit drugs are abused. Euphoria is defined as an intense feeling of well-being, elation, happiness, excitement, and joy. However, there are no euphoric symptoms listed in the

adverse effects of for this drug. Pharmacologically-induced euphoria is most commonly seen with stimulants, opioids, and cannabinoids.

4. A 42-year-old woman comes to the physician because of a persistent inability to fall asleep and/or stay asleep each night (4-5 nights per week) over the past 8-9 months. She states that she is continually exhausted during the day and her work as a pharmacist is "really suffering." She indicates that she normally works 3 shifts, 12 hours each, plus one 8-hour shift per week. She denies using alcohol or illicit drugs. Physical examination is normal. Based on the information presented in the drug ad for ZzzKadia, which of the following is the most appropriate initial statement to the patient?

   (A) "Before I prescribe you a prescription medication for your insomnia, let's try some natural remedies found at a local health and wellness store."

   (B) "I am thinking that ZzzKadia would be perfect for you. Although it does have some serious side effects, you are not likely to experience them due to your relatively young age."

   (C) "I do not recommend prescribing you any medication at this time since you do not have insomnia disorder."

   (D) "I do not recommend ZzzKadia for you; however, suvorexant or zaleplon may be an appropriate treatment option."

   (E) "ZzzKadia is a new drug that will be perfect for you; however, it does have some serious side effects."

The correct answer is D. According to the DSM-5, the diagnostic criteria for insomnia disorder are as follows:

- Predominant complaint of dissatisfaction with sleep quality or quantity associated with 1 or more of the following: difficulty initiating sleep, difficulty maintaining sleep, or early-morning awakening with inability to return to sleep
- Sleep disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- The sleep difficulty occurs at least 3 nights per week.
- The sleep difficulty is present for at least 3 months.
- The sleep difficulty occurs despite adequate opportunity for sleep.
- The insomnia is not better explained by another disorder or is attributed to effects of a substance (drug abuse, medication).

Based on this information, the patient meets the DSM-5 criteria for insomnia disorder, which is commonly treated with pharmacological therapy. Although ZzzKadia is indicated for treatment of insomnia disorder (as seen in the Indications section), this drug would not be recommended for this patient, since she works 12-hour shifts and the average total sleep time with ZzzKadia is 11.2 hours. Furthermore, the drug has a half-life of approximately 10 hours. Assuming that the patient was able to awaken earlier than 11.2 hours, the pharmacological effect (and CNS side effects) would likely be present in the patient while she was working in the pharmacy. However the average total sleep time with both suvorexant and zaleplon are 6.3 and 6.7 hours, respectively. Either of these medications (currently approved for insomnia by the FDA) would likely be an appropriate treatment option.

Choice A is incorrect since you would not see non-FDA approved medications on the exam.

PART III

Patient Safety & Quality Improvement

Clinical Applications of Patient Safety and Quality Improvement

24

Learning Objectives

- ❑ Define the principles of patient safety, system-based practice, and continuous quality improvement
- ❑ Recognize and classify the different types of medical error
- ❑ Describe the types of reporting systems that can identify and analyze medical errors

PRINCIPLES OF PATIENT SAFETY

Case: Within the past 2 years, a major tertiary care referral hospital experiences separate cases of a blood transfusion reaction due to incompatibility, 2 inpatient falls leading to significant injury, a wrong-site surgery, and a medication-dosing error resulting in a patient death.

- What is the most probable single underlying cause behind these medical errors?

  Systems failures due to the complexity of health care delivery

Health care is not a single system, but rather multiple systems which all interact. These clinical microsystems are defined as a group of clinicians and staff working together with a shared clinical purpose to provide health care for a population of patients. Individual health care organizations contain multiple microsystems that evolve over time. It is the complexity of these systems that predispose patients to harm from medical error.

Health care in the United States is capable of achieving incredible results for even the most severely ill patients. However, it does not do so reliably and consistently. Medical errors plague our health delivery systems. In 1999, the Institute of Medicine (IOM) estimated that 44,000–98,000 patients die each year in the United States from preventable medical errors; some of the more recent estimates report an even higher rate of death. This places health care as the third leading cause of death in the United States alone. In addition to the toll that this takes in the form of human suffering, medical errors also represent a significant source of inefficiency and increased cost in the health care system.

The causes of these adverse events are not usually from people intentionally seeking to harm patients, but rather from the complexity of the health care system together with the inherent capability for human error. The causes of these errors are varied and can include failures made in administering medication, performing surgery, reporting lab results, and making a diagnosis, to name a few. The most severe of these medical errors are referred to as **sentinel events.** A sentinel event is an adverse event in which death or serious harm to a patient has occurred; it usually refers to an event that is not at all expected or acceptable (e.g., operating on the wrong patient or wrong body part, abduction of an infant from a hospital, patient suicide while admitted to the hospital). The choice of the word *sentinel* reflects the severity of the injury (e.g., amputation of the wrong leg) and the likelihood that investigation of such an event will reveal serious problems in current policies or procedures.

It is unacceptable for patients to suffer preventable harm caused by a health care system whose purpose is to provide healing and comfort. Improving patient safety is the responsibility of every health care professional and requires a comprehensive team effort. Collectively, health care needs to learn from past errors (e.g., root cause analysis) and develop systems of care that prevent future errors from harming patients (e.g., checklists, electronic health records, structured communication).

Systems in health care delivery can be redesigned to **make it difficult for health care personnel to do the wrong thing** and **easier for them to consistently do the right thing**.

UNDERSTANDING MEDICAL ERROR

Classifications of Medical Errors

Medical errors can be classified as **errors of commission** (doing something wrong) or **errors of omission** (failing to do the right thing). Errors of omission are more difficult to recognize than errors of commission, but are thought to represent a larger percentage of medical errors.

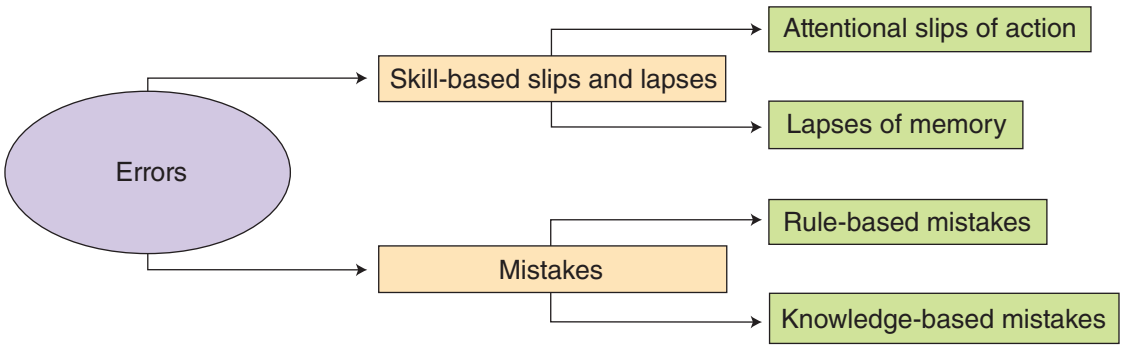
Examples are ordering a medication for a patient with a documented allergy to that medication (**error of commission**), or failing to prescribe venous thromboembolism prophylaxis for a patient undergoing hip replacement surgery (**error of omission**).

> Case: A 47-year-old man presents to the outpatient clinic with complaints of shoulder pain and is diagnosed with arthritis. The clinician treating him administers a shoulder corticosteroid injection without reviewing the patient's medication list prior to the procedure. The patient has been taking Coumadin for atrial fibrillation and develops hemarthrosis.

- Error classified as a **lapse or omission**

Lapses are missed actions or omissions (e.g., forgetting to monitor serum electrolytes in a patient undergoing diuresis for congestive heart failure). Lapses are not directly observable (i.e., you cannot directly 'see' a lack of memory). **Slips** are observed actions that are not carried out as intended (e.g., accidentally injecting a medication intravenously when it was meant to be given subcutaneously). **Mistakes** are a specific type of error brought about by a faulty plan or where the intended action is incorrect (e.g., performing a barium swallow on a patient with suspected esophageal perforation).

The figure below clarifies the relationship further.



Case: After an unexpected 3-hour delay in the operating room due to a problem in the electrical system, an operating room team rushes to get started in order to complete the scheduled elective procedures. The team elects not to perform the mandatory sponge count at the end of the first surgery in order to get the next case started sooner. The patient returns 2 weeks later with abdominal pain and is found on x-ray to have a retained foreign object (a sponge) in the abdominal cavity.

- Adverse event due to **"violation" in policy**

Violations are conscious failures in adhering to policy or regulation. Violations differ from slips, lapses, and mistakes because they are deliberate actions, i.e., intentionally doing something against the rules. Reasons for violations may include time constraints, unfamiliarity with policy, or motivation by personal gain. A health care professional may consider that a violation is well-intentioned; however, if it results in an adverse event it would still technically constitute a "violation" rather than an error.

Case: A 65-year-old man presents to the emergency department with sudden epigastric pain. He has a history of alcoholism, and the treating physician suspects a diagnosis of pancreatitis. Despite the fact that the patient denies alcohol use for several years, has normal blood levels of pancreatic enzymes, and has an abnormal EKG, he is treated for pancreatitis and the actual diagnosis of myocardial infarction is delayed.

- Error due to **"anchoring bias"**

Anchoring bias describes when a clinician relies on and clings steadfastly to the initial diagnostic impression, despite subsequent information to the contrary. In many cases the features of a patient's presentation allow the clinician to make a correct initial diagnostic impression; however, in certain cases subsequent developments in the patient's course will prove inconsistent with the first impression. Anchoring bias refers to the tendency to hold on to the initial diagnosis, even in the face of disconfirming evidence.

Case: A 33-year-old woman with a breast lump is asked if it is tender. When she says that it is tender, the clinician concludes that the diagnosis is a cyst. No further history is obtained and the clinician fails to realize there has been an increase in size, associated adenopathy and fixation to the chest wall (hence the tenderness), all suggesting breast cancer.

- Error due to **"confirmation bias"**

Confirmation bias may accompany anchoring and refers to the tendency to focus on evidence that supports an initial diagnosis, rather than to look for evidence that refutes it or provides greater support to an alternative diagnosis.

Case: A 24-year-old sexually active woman is seen by her ObGyn physician for complaints of abdominal pain. She is evaluated briefly and treated for a UTI without any other tests being performed. The next day, the patient presents to the emergency department and is diagnosed with a ruptured appendicitis.

- Error defined as **"premature closure"**

Premature closure is acceptance of a diagnosis before it has been fully vetted by considering alternative diagnoses or searching for data that contradict the initial diagnosis. In this case the physician finds a cause that fits the clinical picture and ceases to search for other diagnostic possibilities.

Case: A 4-week-old infant is brought to the emergency department by his parents after he develops an episode of emesis with an observed period of apnea. Three other infants were seen there earlier this week with the flu. The infant is discharged home with instructions for flu management, but the parents return with him later, reporting that he had another episode of apnea. The patient is further evaluated and subsequently transferred to the children's hospital with the clinical diagnosis of apnea from gastroesophageal reflux.

- Cognitive error classified as **"availability bias/heuristic"**

Availability bias/heuristic is the tendency to make the diagnosis of a current patient biased by recent or vividly recalled cases or events, rather than on prevalence or probability.

Case: During her third visit to an outpatient clinic for shortness of breath, a 57-year-old woman with previously documented pneumonia is treated with antibiotics and sent home. She later presents to the emergency department with exacerbation of dyspnea and is admitted to the medical service, where she is found to have hypoxia from heart failure.

- Error due to **"diagnosis momentum"**

Diagnosis momentum is a bias that occurs when the diagnosis considered by one clinician becomes a definitive diagnosis as it is passed from one clinician to the next; it then becomes accepted without question by clinicians down the line. It is the medical equivalent of "following the crowd."

Case: A patient with a known heroin addiction presents with abdominal pain. The treating physician assumes the pain to be a sign of opiate withdrawal and manages the patient accordingly with admission to the inpatient med-psychiatry ward. Later during the hospital stay the patient's pain increases, and he develops peritonitis from a missed bowel perforation.

- Error related to **"framing effects"**

Framing effects: Diagnostic decision-making unduly biased by extraneous and collateral information. This can lead to diagnostic error by allowing the way the story is framed to influence the diagnosis.

Human Factors that Cause/Influence Medical Errors

An understanding of medical error requires comprehension of the personal situations and factors associated with the risk of error. Human beings have limited memory and attention capacity. People can make errors when distracted or overtasked. The risk of error is exacerbated by conditions of fatigue, stress, and illness.

Case: A 9-year-old-boy is admitted to the pediatric oncology service for the treatment of a hemolytic malignancy and is started on chemotherapy ordered from the pharmacy. The hospital pharmacist is working a double shift because 2 other pharmacists called in sick. The hospital is particularly busy, and the pharmacist has not had a break all day. He accidentally sends the wrong dose of chemotherapy to the floor, after which the patient develops a hypotensive reaction. The patient is successfully resuscitated with fluids and supportive care.

- What factors likely contributed to this adverse patient event?

  Poor working conditions and fatigue

The risk of medical error is increased when health care professionals work under less than ideal circumstances, especially when well-designed safety systems are not in place. Poor working conditions include:

- Lack of supervision
- Time pressures
- Poor safety procedures (e.g., lack of safety policies)
- Poorly designed human-equipment interfaces (e.g., infusion pumps that are difficult to program)
- Inadequate information (e.g., missing or outdated labs, illegible written orders, failure to communicate a critical change in patient status, language barriers)

A helpful acronym which can be used by health care providers to assess their suitability to provide patient care is **IM SAFE**.

Illness
Medication
Stress
Alcohol
Fatigue
Emotion

The following actions have been demonstrated to limit errors caused by human factors.

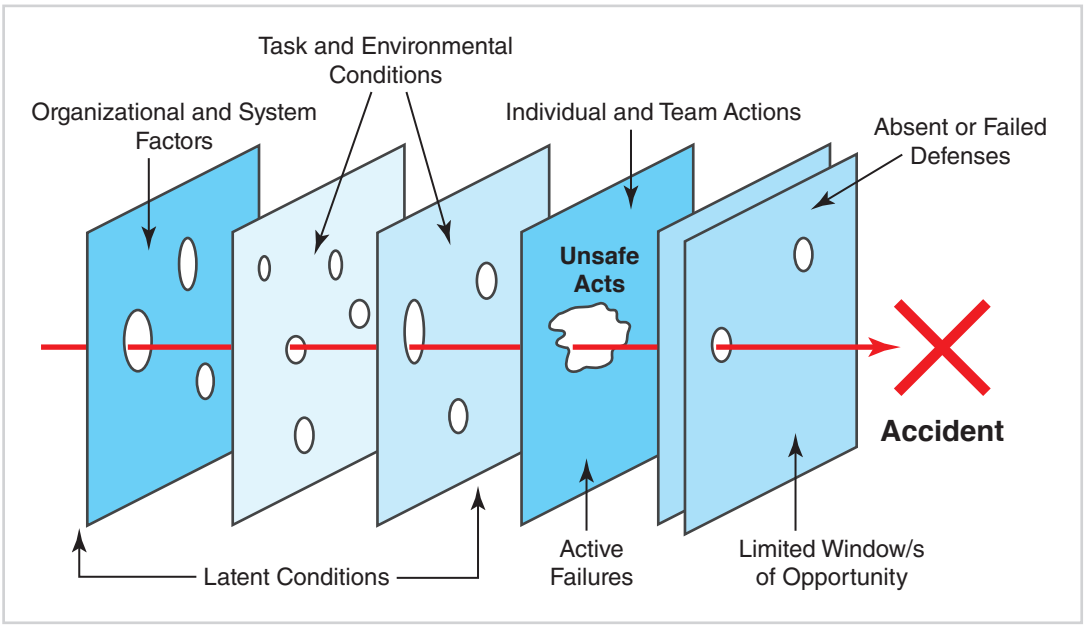
- Avoid reliance on memory or vigilance.
- Simplify processes when possible.
- Standardize common procedures and processes.
- Routinely use checklists.

SYSTEMS-BASED PRACTICE

Lessons from high-reliability organizations (e.g., aviation, nuclear power plants) emphasize the importance of approaching errors on a **systems level** rather than a personal level with blame. It is easier to redesign the conditions under which people work than to attempt to change fallible human nature. When a system fails (i.e., medical error occurs), the immediate question should be **why did it fail**, not "who caused it to fail."

A classic example of a systems-based approach to patient safety is the removal of concentrated potassium from general hospital wards. This action was intended to prevent the inadvertent preparation of IV solutions with concentrated potassium, an error that had produced small but consistent numbers of deaths for many years. This particular approach is called a "forcing function," where the system is redesigned in a way that forces an individual to avoid making the error due to process design, rather than relying on individual memory. Think of a car that won't allow you to start the engine unless your foot is on the brake.

The "Swiss-cheese model of error" (James Reason, 1991) helps to identify the multiple factors that can often contribute to an error resulting in patient harm.



The layers represent barriers that prevent human error from causing patient harm. In a perfect world, these defenses would be impenetrable and patients would always be safe. In reality, these defenses have holes (hence, "Swiss cheese"), which represent latent hazards (e.g., poor system design, lack of supervision, equipment defects). Occasionally the holes line up and a patient is injured.

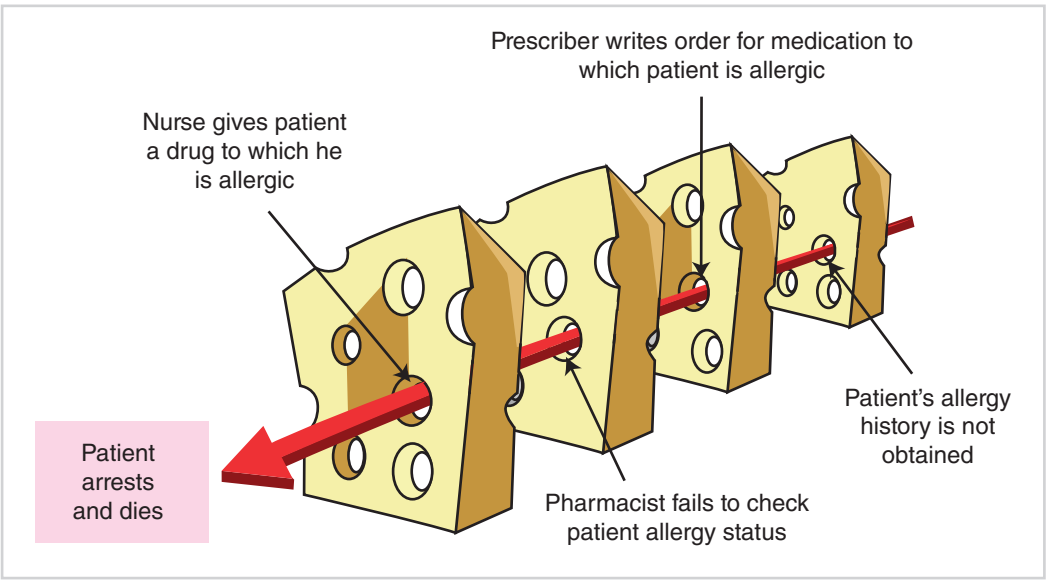
Patient harm can be avoided by building systems with successive layers of protection (e.g., awareness, alarms, policies) and removal of latent errors (i.e., plug the holes).

Case: A 45-year-old man presents for treatment of acute sinusitis. He is prescribed antibiotics, after which he suffers a severe allergic reaction requiring hospitalization. Despite attempts of resuscitation, the patient sustains a cardiac arrest and dies. Later review of his medical record reveals a documented allergy to the antibiotic that was prescribed.

- How do we learn from this event to prevent a similar occurrence in the future?

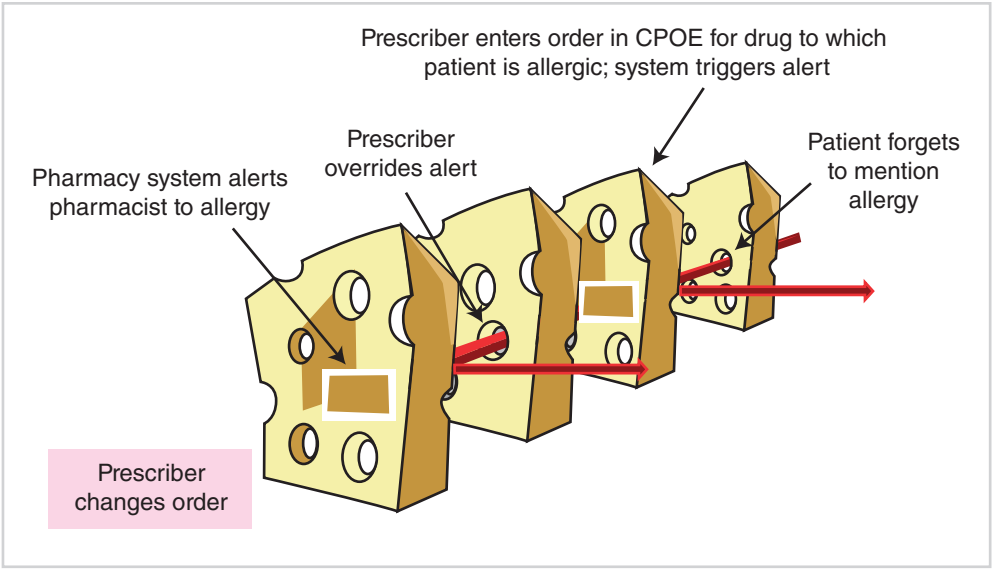
Error disclosure and analysis

An example of the "Swiss cheese model" follows below.



This example details a **medication error**. The patient's medication allergy is not obtained in the initial history, thus leading to the wrong medication being prescribed by the clinician, filled by the pharmacist, and administered by the nurse. The final result is the patient's death.

Applying "systems-thinking" here, the question to be addressed is, "How can the system be redesigned so it is able to absorb the error before it reaches the patient?"



A systems-based redesign seeks not to *remove* the possibility of error, but rather to **create/reinforce barriers to harm**. For this case, one example would have been to implement a computer physician order entry (CPOE) based on the patient's electronic health record, which

could have alerted the prescriber and pharmacist to the allergy. Even if the prescriber somehow ignores the CPOE alert, an additional system in pharmacy serves as a back-up to prevent the medication error.

Disclosure of Medical Errors

Known medical errors should be openly disclosed to the affected patient or their families. During error disclosure, it is crucial to prepare the appropriate environment for disclosure. Be sure to arrange to have the proper time, place, and people involved, including arrangement of follow-up care and psychosocial support.

> Case: A 29-year-old man is brought to the emergency department after falling from a ladder. He is evaluated in the trauma bay and subsequently admitted to the hospital with a bilateral calcaneal fracture and stable L4/L5 compression fracture of the spine. The nurse notices that the blood pressure cuff used on the patient had blood stains on it from a prior patient treated for a motor vehicle collision. The prior patient was known to have hepatitis C. Somehow the cuff was not changed or cleaned before being used on the new patient, thus potentially exposing him to hepatitis C.
>
> • What information should be conveyed to the patient who was exposed?

An error disclosure should include the following 3 elements:

1. Accurate description of the events and their impact on the patient
2. Sincere apology showing care and compassion
3. Assurance that steps are being taken to prevent the event from happening in the future

Often the most senior physicians responsible for the patient and most familiar with the case will make the official disclosure.

Note

Be aware of the **other victims** of medical error: the health care professionals involved in the adverse event. Studies report that these individuals often have strong feelings of self-doubt, shame, and fear, and in fact directly blame themselves for the event.

Without the proper support, this can lead to significant depression, and in extreme cases, suicide. It is important to support colleagues who have been involved in medical error and to seek counseling and support if you yourself have been involved in an adverse event leading to significant patient harm. As much as possible, the goal is to learn from the error and move on.

QUALITY IMPROVEMENT PRINCIPLES

Only 5% of patient harm is directly due to individual incompetence or poor intentions. People need to be accountable, but system-based changes are needed to truly transform care. Blaming individuals and taking punitive actions for honest mistakes/errors do little to improve the overall safety of the health system. The most effective approach is to **find out how the error happened**, rather than who did it, and then **fix the system** to prevent a similar error from causing harm to patients in the future.

> Case: An 82-year-old man has a lumbar epidural catheter placed as part of his anesthesia for an elective hip replacement. The orthopedic team places the patient on anticoagulation for venous thromboembolism prophylaxis. Following surgery, the anesthesia resident removes the epidural catheter, unaware that the patient is still receiving anticoagulation. Two days later, the patient develops an epidural hematoma and sustains paraplegia.

- What should be done with the intern to improve safety in the future?

  Find out *how* the intern made this error (i.e., how the system allowed the error to occur and result in harm to the patient) and then fix the system to prevent a similar error from causing injury to patients in the future.

Error Reporting

Collecting data on medical errors is essential for improving patient care. Reporting errors provides this data and allows opportunities to improve care by learning from failures of the health care system. Error reporting is facilitated by

- Anonymous reporting
- A simple and easy-to-use system
- Timely feedback
- Absence of punitive actions

Note that while "near misses" do not necessarily need to be disclosed to patients, they should be reported to the system so they can be studied and used to inform system changes. It is important to prevent what was a "near miss" this time from potentially harming a patient in the future.

Root Cause Analysis

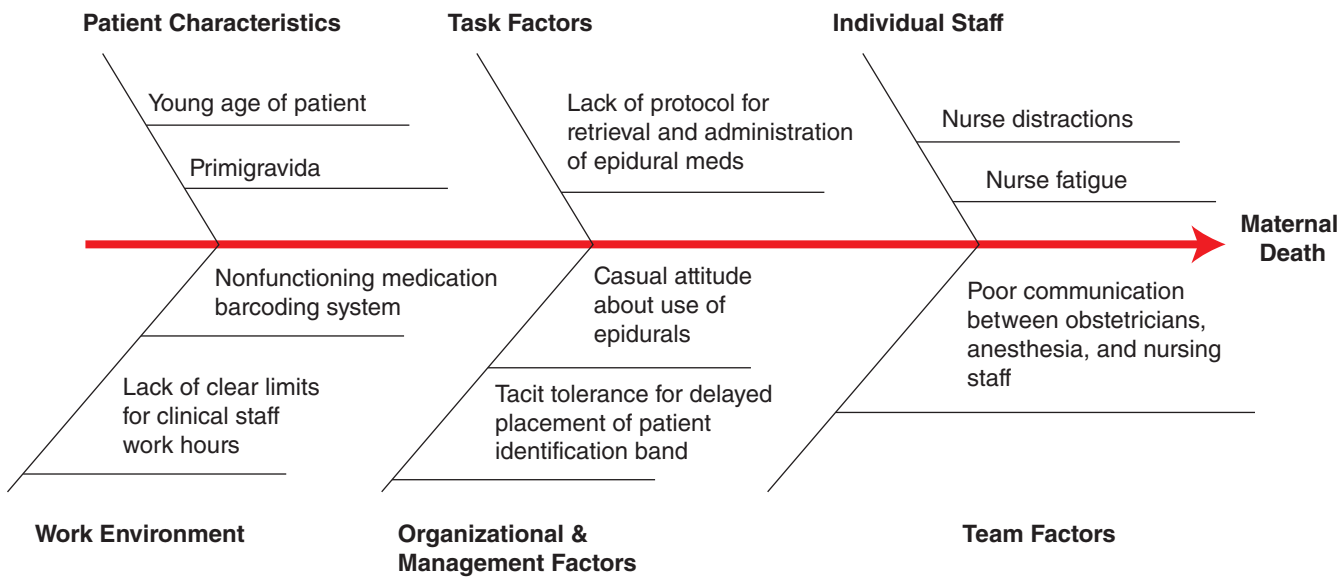
"Root cause analysis" (RCA) is a retrospective approach to studying errors. It allows a team to identify problems in the system or process of care. It should be conducted by a knowledgeable team (consisting of representatives from all the specialties/professions involved in the event), focus on systems/process analysis rather than individual performance, and identify potential improvements that can be made to reduce the chance of similar errors in the future.

Case: A 16-year-old patient goes into labor and is admitted to the hospital for delivery. During the process of her care, an infusion intended exclusively for the epidural route is erroneously connected to the peripheral IV line and infused by pump. Within minutes, the patient experiences cardiovascular collapse. A cesarean section results in the delivery of a healthy infant, but the medical team is unable to resuscitate the mother.

- Describe an effective approach to studying this error so that future cases of patient harm are prevented.

  Root cause analysis

The process of root cause analysis is often supported by the creation of a fishbone diagram (also known as a "Cause and Effect" or Ishikawa diagram) is used to explore all the potential causes that result in a poor outcome. An example is as follows:



In the case presented here, systemic problems identified by the RCA would include medications being kept in the room, communication problems, inexperienced staff, and technology failures. Many solutions are then generated, including the use of barcode scanning and changing the current medication ordering and dispensing policy. Another consideration would be to add a "forcing function," by redesigning the Luer lock on the epidural bag so it is unable to be connected to an IV line.

Failure Mode and Effects Analysis

The Failure Mode and Effects Analysis (FMEA) is a systematic tool that allows practitioners to anticipate what might go wrong with a device, product, or process; determine the impact of that failure; and determine the likelihood of failure being detected before it occurs. Unlike the retrospective nature of RCA, the FMEA is a proactive approach to patient safety. It produces a risk priority number (RPN) based on the probability and relative impact of a failure. The higher the RPN, the higher the priority for corrective action.

$$\text{RPN} = \textbf{Severity of the effect} \times \textbf{Probability of occurrence of the cause} \times \textbf{Probability of the detection}$$

For example: inadvertent esophageal intubation during elective surgery can severely affect patient outcome (rating of 10), but it has a low level of occurrence (2) and can be detected fairly easily (3).

Therefore, RPN for this failure mode = $\mathbf{10 \times 2 \times 3 = 60}$.

BUILDING A SAFER HEALTH SYSTEM

In 2001 the IOM provided 6 aims to improve patient safety and quality; health care should be **S**afe, **T**imely, **E**quitable, **E**fficient, **E**ffective, and **P**atient-centered (STEEEP). Basic concepts for building a health care system that achieves these aims include:

- Standardize care whenever possible
- Reduce reliance on memory (e.g., using checklists for important steps)
- Use system-based approaches to build safety nets into the health care delivery process to compensate for human error
- Openly report and study errors (e.g., using RCA to learn from error)
- Engage with patients (i.e., patient education is a powerful tool for safety)
- Improve communication and teamwork

Surgery

Patient safety in surgery is similar to patient safety in non-surgical settings and involves many of the same issues including medication error, hospital-acquired infection (HAI), and readmissions. It also includes some errors specific to procedures including wrong-site surgery, retained foreign objects, and surgical site infections.

A **wrong-site procedure** is an operation or procedure done on the wrong part of the body or on the wrong person. Another variation of this adverse event is performing the wrong procedure on a patient. Wrong-site procedures are rare and preventable, but they do still occur. Using a standard system to confirm the patient, site, and intended procedure with the medical team and patient before the procedure starts is a widely employed method of reducing or eliminating these types of errors.

> Case: A 59-year-old man with unresectable lung cancer presents to the emergency department with acute shortness of breath. A chest radiograph demonstrates a right sided malignant pleural effusion. The thoracic surgeon intending to drain the pleural effusion mistakenly places the chest tube on the left side after reading an x-ray of another patient. Post-procedure chest x-ray shows a persistent pleural effusion on the right lung. A second chest tube is then placed, this time in the patient's right chest. The patient remains stable and his breathing improves. The left chest tube is removed after confirmation that there is no air leak. There are no further sequelae.
>
> - What is one way this adverse event could have been prevented?
>
> **Pre-procedure checklist or team brief**

A team of researchers and safety experts supported by the World Health Organization's "**Safe Surgery Saves Lives**" program developed a surgical safety checklist designed to improve team communication and consistency of care with the intent of reducing complications and deaths associated with surgery. The premise of the safe surgical checklist is that many common surgical complications are preventable. Implementation of the checklist was associated with significant reductions in the rates of death and complications including wrong-site surgery.

Among other benefits, the surgery checklist helps ensure appropriately administered antibiotic prophylaxis, which reduces the incidence of surgical wound infection. The timing of antibiotic administration is critical to efficacy.

- The first dose should be given preferably within 30 minutes before incision.
- Re-dosing at 1 to 2 half-lives of the antibiotic is recommended for the duration of the procedure.
- In general, postoperative administration is not recommended.

Antibiotic selection is influenced by the organism most likely to cause a wound infection in the specific procedure.

Common Elements of the Safe Surgery Checklist

- Confirm patient identity, planned procedure, and marking of site
- Review patient allergies
- Ensure necessary equipment is present (e.g., pulse-oximetry)
- Introduce team members to each other
- Review critical steps of the procedure
- Address need for preoperative antibiotics
- Determine airway risk
- Determine estimated blood loss

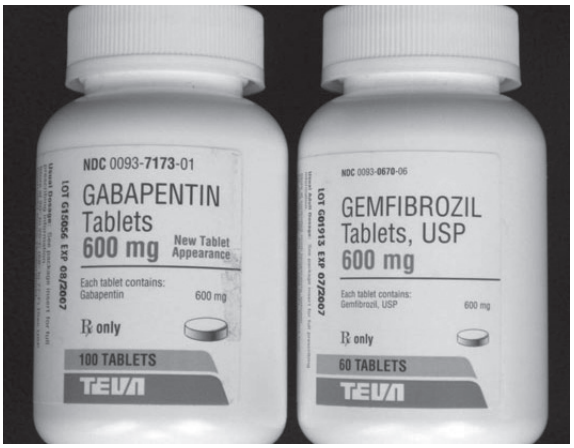
Medications

Medication errors occur when a patient receives the wrong medication or when the patient receives the right medication but in the wrong dosage or manner (e.g., medication given orally instead of IV, or correct medication given at the wrong time). These errors represent one of the most common causes of preventable patient harm.

> Case: A 54-year-old woman (Susan Jones) is admitted to the hospital and diagnosed with metastatic breast cancer for which chemotherapy is administered. During her hospitalization she mistakenly receives an anticoagulation medication intended for the woman next to her in the room who has a similar name (Suzanne Jonas). The mistake is recognized after the first dose and the medication discontinued without any complications. Later during the same admission, she is inadvertently given an overdose of a narcotic when the verbal order for pain medication is administered intravenously instead of orally. She experiences lethargy and hypotension, which resolve with supportive care during a brief stay in the ICU.
>
> - What are the risk factors contributing to the occurrence of these medication errors?

Several factors can increase the risk of medication errors:

- Inadequate confirmation of patient identity prior to medication administration
- Look-alike and sound-alike (rifampin/rifaximin) medications



- Look-alike medications
- Illegible handwritten prescriptions/orders can result in a pharmacist or nurse administering the wrong drug or wrong dose of medication
- Use of certain abbreviations can result in misinterpretation of the order

The Joint Commission created a "**Do Not Use**" list of abbreviations for health professionals.

Official "Do Not Use" List[1]		
Do Not Use	***Potential Problem***	**Use Instead**
U, u (unit)	Mistaken for "0" (zero), the number "4" (four) or "cc"	Write "unit"
IU (International Unit)	Mistaken for IV (intravenous) or the number 10 (ten)	Write "International Unit"
Q.D., QD, q.d., qd (daily) Q.O.D., QOD, q.o.d, qod (every other day)	Mistaken for each other Period after the Q mistaken for "I" and the "O" mistaken for "I"	Write "daily" Write "every other day"
Trailing zero (X.0 mg)* Lack of leading zero (.X mg)	Decimal point is missed	Write X mg Write 0.X mg
MS MSO4 and MgSO4	Can mean morphine sulfate or magnesium sulfate Confused for one another	Write "morphine sulfate" Write "magnesium sulfate"

[1] Applies to all orders and all medication-related documentation that is handwritten (including free-text computer entry) or on pre-printed forms.

Source: jointcommission.org

The "**5Rs**" describe a strategy used to help prevent medication error by confirming the following 5 items prior to administering any medication.

- Right drug
- Right patient
- Right dose
- Right route
- Right time

Performing **medication reconciliation** (a review of the patient's complete medication list during any transition of care) is also intended to prevent inadvertent inconsistencies in the medication regimen.

Other systems changes that have saved countless lives:

- Removal of high-risk medications from certain clinical settings
- "Unit dose administration," in which medications packaged in ready-to-use units are prepared by the pharmacy and delivered to the clinical floor (this practice has resulted in fewer medication errors compared with having nurses perform mixing and dispensing on the floor)

The **integration of information technology** has also helped to reduce medication errors. Studies have shown that Computerized Physician Order Entry (CPOE) is an effective means of reducing medication error. It involves entering medication orders directly into a computer system rather than on paper or verbally. CPOE can decrease prescribing errors by automatically alerting the prescriber or pharmacist to allergies, potential drug-drug interactions or an incorrect dose.

Other technologies that have been designed to improve medication errors include barcoding to confirm correct patient identity and smart-pumps to prevent inappropriate dosage of IV medications.

Infections

Hospital-acquired infections (HAI) can be avoided. They are preventable, adverse events which may be caused by failing to adhere to evidence-based prevention strategies. Common HAIs include UTI (most common 35-40%), hospital-acquired pneumonia/ventilator-acquired pneumonia (15-20%), surgical site infection (20%), and central line infection (10-15%).

Case: A 42-year-old man has surgery to repair a right inguinal hernia. His post-operative course is complicated by excessive post-op pain requiring IV narcotics. Ten hours after surgery he develops pubic pain. He has not voided since before surgery. A bedside ultrasound confirms a distended bladder indicating acute urinary retention. A urinary catheter is placed by a new nurse who is not familiar with sterile technique. The catheter immediately yields 800 cc of urine and the patient's pubic pain resolves. The patient requests to have the catheter left in place over the next 2 days. On post-operative day 3 the patient develops a fever to 101°C. A urine analysis and culture reveal an acute urinary infection.

- What steps can be taken to reduce the likelihood of this complication?

  (Read suggestions that follow.)

The Comprehensive Unit-based Safety Program to reduce catheter-associated UTIs was a national program supported by the Agency for Healthcare Research and Quality and the Health Research and Educational Trust. Some suggestions from the program on how to reduce UTIs include:

- Minimized indwelling catheter use by using other urine collection means
- Regular use of infection-prevention techniques for catheter placement and maintenance
- Training on urinary management for all care team members
- Daily checks on patients who have a catheter and whether they need it
- Feedback to doctors and nurses about their unit's catheter use and UTI rates

There are some common approaches that can help to reduce other HAI:

- Hand washing
- Use of sterile technique
- Use of preoperative prophylactic antibiotics (SSI)
- Elevating the head of the bed (ventilation associated pneumonia)
- Following evidence-based protocols for central line placement
  - Hand washing prior to procedure
  - Wearing a cap, mask, sterile gown, and gloves
  - Preparation of site with chlorhexidine
  - Use of sterile barrier
  - Removal of the line as soon as possible

Pressure Ulcers

Pressure, or decubitus, ulcers are often preventable. Approaches to avoid this complication include performing risk assessments to identify vulnerable patients (e.g. paraplegics, diabetics, malnutrition, immobility, etc.).

Case: A 65-year-old woman with type 2 diabetes and BMI 44 is being treated in the hospital for diabetic ketoacidosis. She has a urinary catheter in place to monitor urine output and does not get out of bed to go to the bathroom. She has refused ambulation or getting out of bed to a chair due to feeling very fatigued. Later during the hospital stay she develops a fever. Physical exam reveals a stage III infected decubitus ulcer over the sacral prominence.

- How could this complication have been prevented?

  By using decubitis ulcer prevention methods

Preventive activities for high-risk patients include:

- Daily inspection of skin
- Appropriate skin care
- Frequent repositioning
- Use of pressure-relieving surfaces (e.g., airbeds)

Patient Falls

Patient falls are a common cause of injury, both within and outside of health care settings. More than one-third of adults over 65 fall each year. Injuries can include bone fractures and head injury/intracranial bleeding, which both can lead to death.

> Case: A 70-year-old woman is admitted to the nursing home after being treated in the hospital for a hip fracture sustained during a fall at home. She had an intramedullary nail placed and is currently able to ambulate with a walker. In addition to her hypertension medication, anxiolytic, dementia pills, and a beta-blocker, she also takes post-operative pain medication every 4-6 hours. The patient was also placed on warfarin for DVT prophylaxis. On her way to the bathroom at night, she slips and falls, sustaining a head injury and significant intracranial hemorrhage.

- What steps can be taken to reduce the risk of serious injury from a fall?

  Fall risk assessment and preventive interventions

Performing a fall risk assessment will help to select patients who can benefit from preventative resources (e.g. one-to-one observation, non-slip flooring, lowering the bed height). It is important to identify patients at high risk of sustaining serious injury from a fall. The following are known risk factors for patient fall:

- Advanced age (age >60)
- Muscle weakness
- Use of >4 prescription medications
- Impaired memory
- Difficulty walking (e.g., use of a cane or walker).

Unplanned Readmissions

Unplanned hospital readmissions following discharge are recognized as a serious cause of decreased quality and often result from complications or poor coordination of care. Improving communication, reinforcing patient education, and providing appropriate support to patients at risk for readmissions are all strategies to reduce unplanned readmissions.

> Case: A 79-year-old patient is admitted to the cardiology service and treated for acute CHF. He is started on a new medication regimen, including a diuretic that relieves his symptoms and improves his cardiac function. He is discharged home, though he returns to the hospital 10 days later with another episode of CHF. During the readmission, the team notices that the patient never filled his new prescriptions and was not taking the prescribed diuretic while at home.

- What actions can be taken to prevent this from happening again?

Recommendations to improve the discharge process and prevent readmissions are as follows:

- Provide timely access to care following a hospitalization
- Communicate and coordinate care plan with patients and other members of the care team
- Improve the discharge planning and transition processes
- Ensure patient education and support to optimize home care

Teamwork

Providing safe health care relies on health care professionals working together as a team. Well-functioning teams deliver higher quality and safer care. The need for improved teamwork has led to the application of teamwork training principles, originally developed in aviation, to a variety of health care settings. Simple changes to behavior and culture have had a profound impact on the culture of teamwork and safety in patient care.

> Case: A resident responds to a cardiac code 10 minutes late because he was not aware that he was on code-duty. Upon arrival the patient is actively having chest compressions performed by a physician assistant. A nurse brings in the cardiac arrest cart and a respiratory technician places on oxygen mask on the patient and begins bag-mask ventilation. The resident asks for a blood pressure and heart rate to be checked. The respiratory tech and physician assistant both attempt to find a pulse on the patient's wrist, interrupting chest compressions and ventilation. The nurse simultaneously lowers the bed to place electrodes for an ECG, which makes the oxygen mask fall off to the floor. The ECG demonstrates ventricular fibrillation and the resident calls to "shock the patient." No one is certain how to work the defibrillator. The patient expires.
>
> - How can teamwork be improved to achieve a better outcome during the next cardiac code?

Effective teams share the following characteristics:

- Common purpose/shared mental model
- Measurable goals
- Effective leadership
- Effective communication
- Mutual support
- Respect the value of all team members

Briefs and **huddles** are effective tools for teamwork. The team *brief* is used for planning and is a short "time-out" prior to starting the delivery of care in order to discuss team formation, assign essential roles, establish expectations and climate, and anticipate outcomes and likely contingencies. The *huddle* is used for team problem-solving, and is performed on an ad hoc basis to reestablish situational awareness, reinforce plans already in place, and assess the need to adjust the plan.

Clinical Communication Skills

Communication failures have been identified as a root cause in the majority of serious patient safety events. Patient safety and quality in health care improve when physicians communicate effectively with colleagues, patients, and families. Several techniques have been developed to enhance clinical communication skills.

Case: A 25-year-old woman is admitted to the ICU following a motor vehicle collision, during which she sustained a significant head injury. She is intubated and monitored for increased ICP. The nurse coming on the night shift notices that the patient's pupils are dilated, and she is uncertain if this is a change in the patient's status. The nurse pages the resident on-call to see the patient. The resident evaluates the patient but does not speak with the nurse and is not aware of the nurse's concern of a change in status. No intervention is taken. The following morning during rounds the neurosurgical team finds the patient brain dead from herniation.

- How could communication be improved to prevent this error?

SBAR is a form of structured communication first developed for use in naval military procedures. It has been adapted for health care as a helpful technique used for communicating critical information that requires immediate attention and action concerning a patient's condition.

The following is an example of SBAR communication:

- **S**ituation: What is going on with the patient? "I am calling about Mr. Smith in room 432 who is complaining of shortness of breath."
- **B**ackground: What is the clinical background or context? "The patient is a 67-year-old man post-operative day 1 from a left total hip replacement. He has no previous history of pulmonary or cardiac disease."
- **A**ssessment: What do I think the problem is? "His breath sounds are decreased bilaterally and his oxygenation is only 87% on room air. He was getting IV Ringer's lactate at a rate of 150 cc/hour, in addition to 5 liters fluid replacement and 4 units of blood in the operating room. I would like to rule out acute pulmonary congestion from fluid overload."
- **R**ecommendation: What would I do to correct it or what action is being requested? "I've already started supplemental oxygen and I feel strongly that the patient should be assessed for pulmonary overload, his fluids stopped, and potentially given a diuretic. Are you available to come in?"

Case: During resuscitation of a cardiac code, the physician running the code determines that epinephrine should be given intravenously. The nurse involved in the code starts an IV, but since no order was given, does not administer the epinephrine. The doctor mistakenly assumes that the drug was administered and that it was not effective in reviving the patient. Precious time is lost until it is realized that no medication has been given.

- What communication technique can be used to avoid this error?

Call out

A **call-out** is a strategy used to communicate important or critical information. The goals of a call-out are to inform all team members simultaneously during team events, help team members anticipate next steps, and help create a shared mental model.

Case: A hospital lab technician phones a nurse to inform him of a critical serum calcium value in one of his patients. The nurse mistakenly hears a different number and believes the calcium to be only mildly elevated. The patient develops a symptomatic arrhythmia and requires transfer to the ICU for further appropriate care.

- How can techniques in effective communication be used to prevent this error?

Check-back

A **read-back or check-back** is a communication technique commonly used in the military and aviation industry and is now increasingly employed in health care to guard against miscommunication. Safety organizations encourage health care professionals to make a routine practice of reading back verbal orders or critical labs to ensure accuracy.

Case: During a clinical rotation on the pediatric ICU, you are invited by the chief resident to observe the operative repair of a congenital heart lesion in the pediatric cardiac surgery operating room. When you arrive in the OR the patient is already intubated and anesthetized, and procedures are underway to prep the patient for surgery. During the start of the case you see that an operative team member inserts the urinary catheter with a clear breach in sterile technique. This is neither noticed by the team member inserting the catheter nor mentioned by anyone else in the room. Being new to this setting, you are unaware whether different practices for sterile insertion are used in pediatric patients.

- What would you do to address your concern?

Critical language is a form of assertive structured communication that provides key words that enable members of the team to speak when patient safety concerns arise. These key phrases are uniformly understood by all to mean "stop and listen to me; we have a potential problem."

The acronym **CUS** is used to remember these key words.

- "I'm **c**oncerned"
- "I'm **u**ncomfortable"
- "I think this is a **s**afety issue"

Speaking up for patient safety is the responsibility of every member of the health care team. It is important to speak up for the patient. It may be intimidating to speak up when you are the most junior member of the team and at times uncertain if a safety issue is actually in question; however, as people with the privilege of caring for others, health care workers have to value our responsibility to the patient above all else. **Speak up if you witness an error or the potential for an error**. Make sure to report adverse events so others can study and learn from them—informing system-based approaches to improving patient safety.

Handoffs

Errors during handoffs and sign-outs can be mitigated by ensuring an accurate and effective transfer of pertinent patient information to the receiving health care professional. This has immediate applications to on-call sign-outs and changes of shift, but it also affects other scenarios such as hospital- and unit-floor-transfers.

Case: A diabetic patient with an ankle fracture is signed-out to the covering intern from a team member in a hurry to leave the hospital. Later that night the patient develops sinus tachycardia thought to be related to pain, and the covering intern orders more pain medication. Unknown to the covering intern, the patient was found earlier to have an incidental pulmonary embolism. This information was forgotten during the hurried sign-out. The patient develops chest pain and dyspnea, and ultimately dies from progression of the PE.

- How can this adverse event be avoided in the future?

  Use an effective hand-off process

An effective handoff encompasses the following principles:

- Active process
- Prioritize sick patients
- Verbal + written
- Have a set system
- Limit distractions
- Allow sufficient time
- Ensure updated information

Quality Improvement Roadmap

Using formal quality improvement methodology is helpful for successfully carrying out improvement projects. Health care teams can benefit from a roadmap for applying the science of improvement to the project management tasks associated with their improvement efforts.

Case: A hospital is interested in reducing the number of medication errors in the inpatient geriatric unit. The current medication ordering system has been in place for 15 years and consists of written orders on slips of paper being sent to pharmacy by pneumatic tubes, and then receiving the medication in a batched collection system on the unit. Nurses are required to then sort through the batched medications to identify the correct one for their patient(s). Over the past year, the severity of the admitted geriatric patients has increased, along with the number of medications required. There have been reports of possible increased rates of medication errors over the past 6 months.

- How will you approach improving the current process?

The methods used to approach quality and process improvement are as follows:

1. Identify the problem.
2. Measure the problem.
3. Organize a team.
4. Flowchart the process.
5. Develop a range of interventions to fix the problem.
6. Measure the impact of the interventions.

The following tools are commonly used in quality improvement:

Flow chart: map of all the steps in the current clinical process being evaluated

- Flow charting a process helps the team clearly see the complexity of the process and the opportunities for improvement.

Pareto analysis: process of rank-ordering quality improvement opportunities to determine which of the various potential opportunities should be approached first

PDSA (plan-do-study-act) refers to a rapid cycle of activities involved in achieving process or system improvement. It is a form of trial and error and consists of planning an intervention, trying it out (i.e. small scale pilot), observing results (e.g. data collection of quality measures), and acting on what is learned (e.g. implement change system-wide or go back to the planning stage with a new intervention).

Measurements of quality include structure, process, outcomes, and balancing measures.

- **Structure** refers to equipment, resources, or infrastructure (e.g., number of ICU beds, certified infectious disease specialist on staff, ratio of nurses to patients)
- **Process measures** relate to an action involved in the care of patients that is believed to be associated with a particular outcome (e.g., use of preoperative antibiotics to reduce surgical site infections, using 2 means of patient identification prior to blood transfusion).
  - Typically easier to measure than outcome measures, and often serve as surrogates to outcomes
- **Outcome measures** reflect results related directly to the patient (e.g., survival, infection rates, number of admissions for heart failure)
- **Balancing measures** monitor for unintended consequences of a change or intervention made to a process or system. Some well-intended interventions can create unanticipated negative results in quality and safety.
  - For example, alarms have been placed on a number of medical devices and equipment to alert for problems (e.g., oxygen saturation falling below a set level). One negative result has been "alarm fatigue." Studies indicate that 85-99% of hospital alarms do not require clinical attention, but failure to respond to the rare critical alarm has resulted in patient death. This is a type of "boy who cried wolf" phenomenon, where the frequency and prevalence of hospital alarms reduces our attention to them. Strategies are in place to customize alarms to alleviate some of the problem.

Quality models are specific techniques used in improving patient care.

Understanding variation. Data is essential for the improvement process. Without data, there is no objective way to measure the success of your interventions. Data can also reveal if your interventions have not worked and you need to try something new.

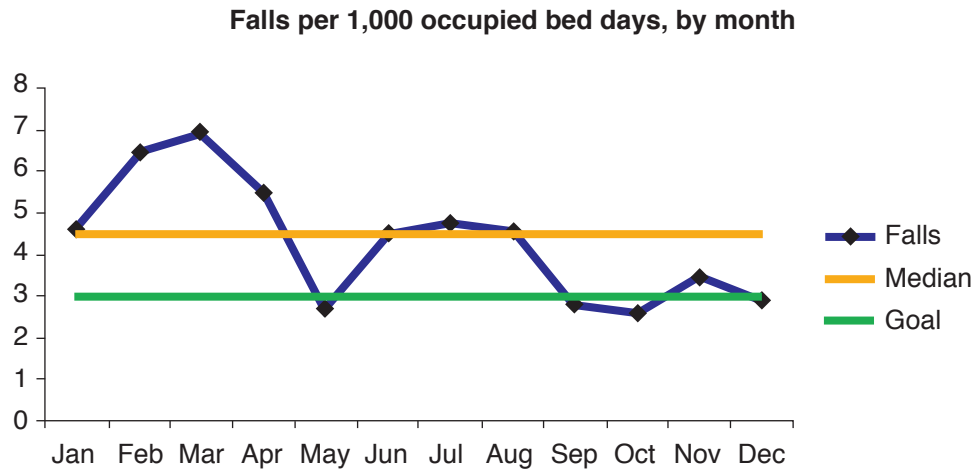
It is important to understand how to correctly interpret data, including the concept of **variation in data**. All data has some level of variation. Walter Shewhart, a pioneer in Total Quality Management, stated that data can be perceived in 2 ways: either as an **indication that something has changed (a trend)** or as **random variation that does not mean a change has occurred**.

Understanding the nature of variation is paramount in decision-making in quality improvement.

- Data should be plotted over time (as seen in run charts and control charts)—both before and after a planned intervention is implemented. This allows assessment to see whether the variation is random or reflective of a pattern/trend indicating that a meaningful change has occurred.
- **Common cause variation** is an inherent part of every process; it is random and due to natural or ordinary fluctuations in the system.
- **Special cause variation** is due to irregular or unnatural causes that are neither predictable nor inherent to the process. Special cause variation should be identified and eliminated before making QI changes to a process.
- Reducing variation improves the predictability of outcomes and helps reduce the frequency of adverse outcomes for patients.

Run chart (time plot): graphical record of a quality characteristic measured over time

- Run charts help the team determine if a change is a true improvement over time or just a random fluctuation.
  - A trend is defined as ≥5 consecutive points constantly increasing or constantly decreasing. If a trend is detected, it might indicate a non-random pattern that should be investigated.
  - A shift is a run containing ≥6 data points all above or all below the median and indicates a non-random pattern that should be investigated.



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Sample Run Chart Plotting Patient Falls

Control chart: similar to run charts but with additional elements of statistical process control; it is used to study how a process changes over time.

A control chart always has a **central line for the average**, an **upper line for the upper control limit,** and a **lower line for the lower control limit**. Using these lines you can determine:

- If the variation is consistent/in control (i.e., data all within the control limits reflecting only common cause variation), OR
- If the data is unpredictable/out of control (i.e., data outside the control limits reflecting special causes of variation)

There are many types of control chart, depending on the statistic analyzed on the chart.

Interventions can take many forms, including automation, standardized process, and checklists. A forcing function is a very effective intervention for patient safety, as it does not rely on human memory or vigilance. A forcing function is an aspect of a design that prevents a target action from being performed. Examples are:

- Computer system that does not allow a drug to be ordered at a dose outside known safety parameters
- Enteral tubing designed to prevents accidental connections with IV ports

Six Sigma is a data-driven, patient-centered approach focused on reducing variability. This organized and systematic method for strategic process improvement uses a step-by-step DMAIC method:

- **Define**: define the problem
- **Measure**: measure key quality metric
- **Analyze**: identify root causes
- **Improve**: determine optimal solutions
- **Control**: strive for sustainability of implemented change

Lean process focuses on removing waste from the process or system and adopting a value-added philosophy of patient care. Value-stream maps are created to optimize activities that add value from the patient point-of-view and remove activities that do not.

In addition to the formal methods described above, the following are steps that any health care practitioner can apply to **improve safety and quality** for patients on a daily basis:

- Follow safety protocols (e.g., hand washing)
- Speak up when there are safety concerns (e.g., medical errors and near misses)
- Practice good communication skills (e.g., SBAR)
- Educate patients about their care
- Take care of yourself (e.g., get appropriate sleep and control stress)
- Practice patient-centered care/recognize opportunities to enhance value for patients

CARE WELL DONE

The following case, from an article written by Dr. Atul Gwande for *The New Yorker*, describes the incredible potential of the health care system. Applying the principles of patient safety and quality improvement to clinical care will enable health care to move closer to the goal of getting it right for every patient, every time.

A 3-year-old girl falls into an icy fishpond in a small Austrian town in the Alps. She is lost beneath the surface for 30 minutes before her parents find her on the pond bottom and pull her up. CPR is started immediately by the parents on instruction from an emergency physician over the phone, and EMS arrives within 8 minutes. The girl has a body temperature of 36° C and no pulse. Her pupils are dilated and do not react to light. A helicopter takes the patient to a nearby hospital, where she is wheeled directly to an operating room. A surgical team puts her on a heart-lung bypass machine, her body temperature increases almost 10 degrees, and her heart begins to beat. Over the next few days her body temperature continues to rise to normal and her organs start to recover. While she suffered extensive neurologic deficits during this event, by age 5 with the help of extensive outpatient therapy, she recovers completely and is like any other little girl her age.

CHAPTER SUMMARY

- Medical errors result from the complexity of health care combined with the reality of human failure. Although accountability and responsibility are important, simply blaming people for errors they did not intend to commit does not address underlying failures in the system and is an ineffective way of improving safety.
- System-based redesigns in health care delivery are required and hold the greatest potential for advancing patient safety and quality improvement.
- Improving communication, teamwork, and the culture of safety are effective methods in improving patient safety.
- Safety is a team effort requiring everyone on the care team to work in partnership with one another and with patients and families.

High Yield Facts

- Systems-based approaches to improving health care are superior to individual-level efforts or blame
- Preoperative checklists can prevent perioperative complications and other adverse events
- Evidence-based clinical protocols have been shown to prevent central line infection
- Limiting the duration of urinary catheters decreases hospital acquired infections
- Head-of-bed elevation and oral care can help prevent ventilator associate pneumonia
- Medication reconciliation helps to prevent medication errors during transitions
- Hand hygiene is an important component of infection control
- Avoiding the use of hazardous abbreviations when writing orders can decrease adverse events from errors
- Computerized physician order entry helps improve medication safety
- Identification of high risk patients is a key step in fall prevention
- Team training and communication are essential components in improving quality and safety

Practice Questions

1. A 36-year-old woman with HIV/AIDS and B-cell lymphoma is hospitalized for *Clostridium difficile*–associated diarrhea. Following treatment, the patient is discharged home with a prescription for a 14-day course of oral vancomycin. She is unable to fill the prescription at her local pharmacy because of a problem with her insurance coverage. While awaiting coverage approval, she receives no treatment. Her symptoms soon return, prompting an emergency department visit where she is diagnosed with toxic megacolon. Which of the following should be addressed in order to bring about changes that improve patient safety?

   (A) Prescribing physician
   (B) Pharmacist
   (C) Insurance company
   (D) Patient
   (E) Discontinuity of care

The answer is E. The main failure in this case occurred upon transition of care from the hospital to home. Addressing the discontinuities in care that arise at the time of transition has the greatest potential to improve patient safety.

Rather than dispensing blame to any of the parties involved in the error (**choices A–D**), focus should be given to implementing systems-based transformations to support patients during a transition (e.g., post-discharge telephone follow-up to identify and resolve potential medication issues early).

2. A 23-year-old man with a history of depression is admitted to the inpatient psychiatry ward after his third attempt at suicide with an intentional drug overdose. The patient is stabilized medically; however, he is put under 24-hour monitoring by the nursing staff due to repeated attempts at self-harm. During a change of shift, there is a mistake in communication and no one is assigned to the patient. The mistake is noticed 15 minutes into the new shift, and a member of the nursing team is assigned to watch the patient. Fortunately, during that 15-minute period, the patient made no attempt to harm himself. Which of the following statements is correct about this event?

   (A) This is a sentinel event and should be reported to the medical board.
   (B) This is a sentinel event and should be reported to the hospital and family.
   (C) This is a near-miss and should be reported to the hospital.
   (D) This is a near-miss and should be reported to the patient and family.
   (E) This is a near-miss and no reporting is required since the patient was not harmed.

The answer is C. The event described is a near-miss; there was an error, which fortunately did not result in patient harm. Most near-misses need not be disclosed to patients or families (**choice D**), however should not be covered up. All near misses should be reported to the hospital so that the error can be studied and thus prevented in the future. A sentinel event (**choices A and B**) is an adverse event resulting in serious or permanent injury to a patient.

3. An 85-year-old woman is being transferred to an acute rehabilitation facility following a hospital admission for hip replacement surgery. Postoperatively during her hospital stay, she is started on deep vein thrombosis (DVT) prophylaxis medication with plans to continue the medication upon discharge. The intern and nurse who are discharging the patient fail to convey this new medication to the receiving treatment team at the rehabilitation center. The patient is not continued on her anticoagulation medication and sustains a DVT, leading to a fatal pulmonary embolus 3 weeks after transfer. Which of the following actions will facilitate quality improvement and the prevention of a similar error in the future?

   (A) Determine which staff member(s) failed to order the medication
   (B) Develop a process to increase the use of medication reconciliation
   (C) Send a memo to all staff about the importance of DVT prophylaxis
   (D) Educate patients about the dangers of DVT following hip surgery
   (E) Conduct monthly audits to monitor medication errors at transitions of care

The answer is B. The goal of quality improvement (QI) is to achieve improvement by measuring the current status of care and then developing systems-based approaches to making things better. It involves both prospective and retrospective reviews and specifically attempts to avoid attributing blame. QI seeks to create systems to prevent errors from happening. In this case, developing a process to increase the use of medication reconciliation would be following the principles of QI. The other interventions in the answer choices are QA-based and/or simply not as effective in creating and sustaining a positive change. Quality assurance (QA) is an older term describing a process that is reactive and retrospective in nature; it is a form of "policing" to ensure that quality standards have been followed. It often relies on audits and traditionally has focused on punitive actions for failures in quality, i.e., determining who was at fault after something goes wrong. QA has not proven to be very effective in transforming care.

Population Health Management 25

Learning Objectives

- ❑ Define population health and value-based care
- ❑ Describe how population health management principles can be put into practice

DEFINING POPULATION HEALTH

What is population health?

Case example: A 65-year-old woman presents to the emergency department at 3:00 AM with the acute onset of an asthma attack. She is treated with steroids and nebulizer treatments to stabilize her respiratory status. This is the third such presentation in the past 9 months. During her course of treatment it becomes evident that the patient is not able to get time off from work to see her primary care physician during clinic hours, did not receive an influenza vaccination this year, and continues to smoke 1 pack of cigarettes per day.

- What population health approaches can help this patient?

  Address the day-to-day factors present at home that impact the patient's health outcomes with asthma

Health care in the United States has traditionally focused on the management of acute medical problems such as trauma, myocardial infarction, and stroke. Incredible advances have been made in these areas and outcomes from acute presentation of disease have steadily improved over the years, with outcomes among some of the best observed in any health system in the world.

However, the health care system here has lagged significantly in the area of disease prevention and health maintenance. Major disparities in access to preventative care services such as prenatal care, cancer screening, and diabetes management; together with social inequalities with respect to patient education and income; as well as persistent individual behaviors such as poor diet, lack of exercise, and cigarette smoking have contributed to the very poor overall health status observed in the United States.

BIG GEMS (mnemonic for determinants of health)

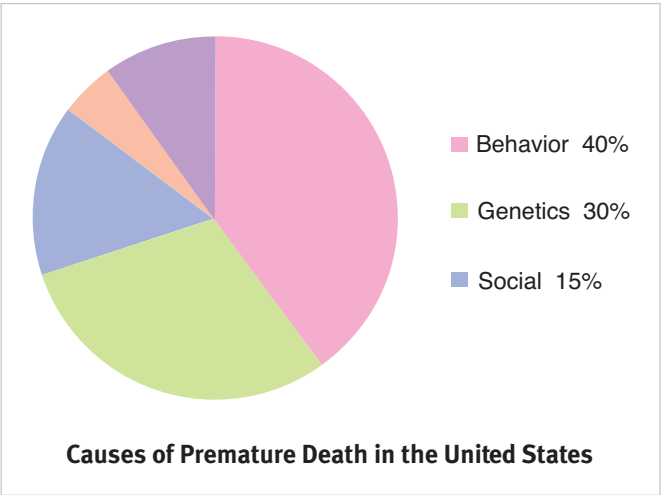
- **B**ehavior
- **I**ncome
- **G**enetics
- **G**eography
- **E**nvironment
- **M**edical care
- **S**ocial-cultural

Problems with quality and variations in health delivery that do not follow evidence-based standards further erode the value of patient care. Ironically, the United States spends more on health care than any other nation in the world, yet ranks among the lowest in health measures, compared to other developed nations. Furthermore, the current rate of health care spending in the United States is unsustainable.

Population health is an approach to health care that addresses both individual and public health concerns in order to achieve optimal patient results. It is an approach to patient care which understands that health is influenced by several factors outside of traditional health care delivery models, including (but not limited to) social, economic, and environmental factors.

Population health management is fundamental to the transformation of health care delivery. Its principles recognize the importance of focusing attention not only on improving individual patient care, but also on improving the health of an entire population. In fact, direct health care accounts for only a small proportion of premature deaths in the United States.

- For example, the leading causes of premature death—smoking (435,000 deaths/year), obesity (400,000 deaths/year), and alcohol abuse (85,000 deaths/year)—are all preventable through interventions driven by population health management.

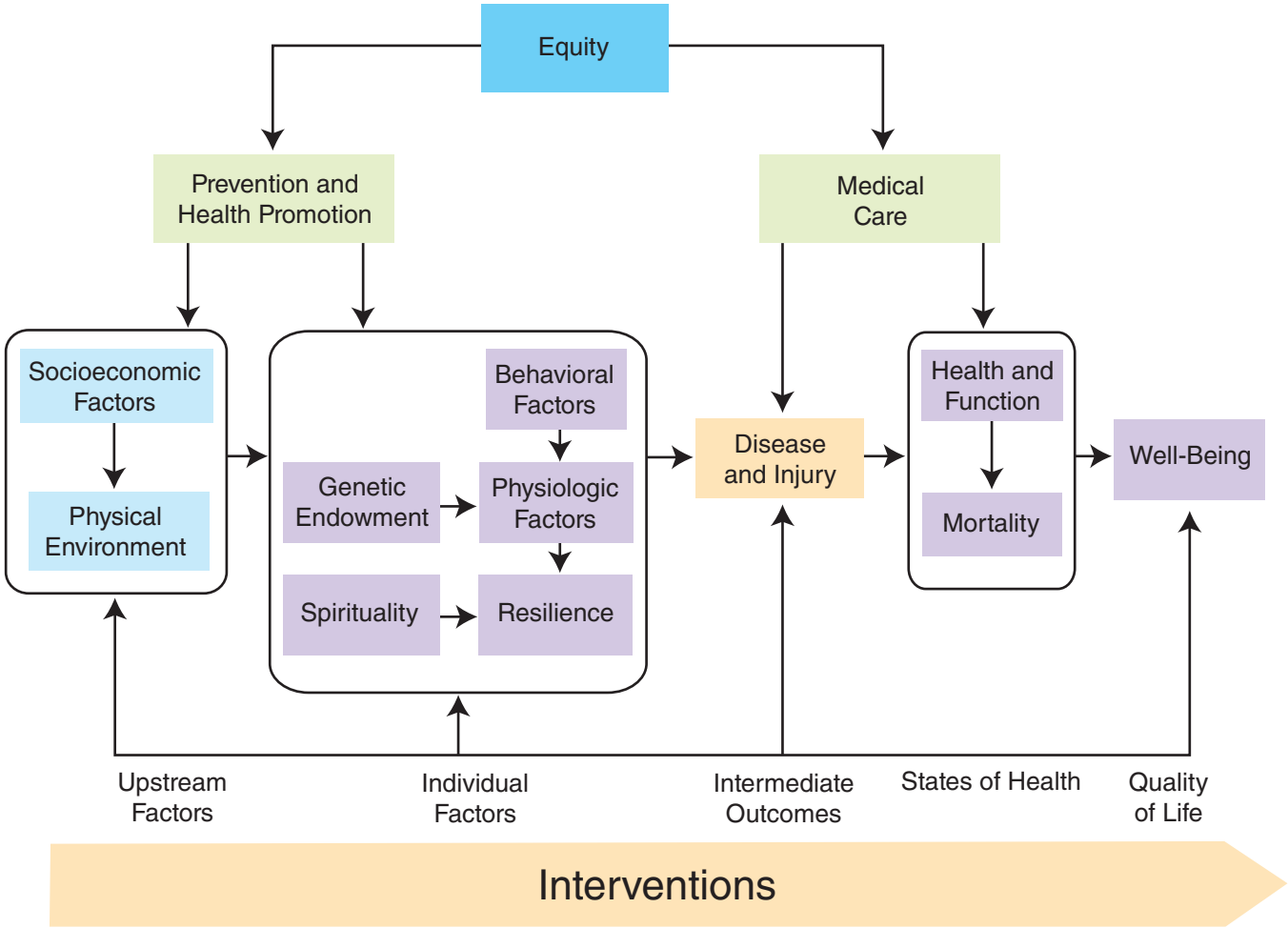


Causes of Premature Death in the United States

Population health management is, in effect, about coordinating care and improving access in order to enhance patient/family engagement and reduce variation in care to achieve better long-term outcomes at a reduced cost. The Institute for Healthcare Improvement (IHI) lists improving the health of the population as one of the 3 dimensions of its Triple Aim approach to optimizing health system performance.

IHI Triple Aim:

- Improve the patient experience of care (including quality and satisfaction)
- **Improve the health of populations**
- Reduce the per capita cost of health care



Source: Adapted from Stiefel M. Nolan KA. Guide to Measuring the Triple Aim: Population Health, Experience of Care, and Per Capita Cost. IHI Innovation Series white paper.Cambridge, Massachusetts: Institute for Healthcare Improvement; 2012. (Available on www.IHI.org)

IHI Population Health Composite Model

Population health management focuses on high-risk patients who are responsible for the majority of health care utilization, while simultaneously addressing preventative and chronic care needs of the entire population. One of the first steps in this process is to define the target population (e.g., a hospital or clinic's entire service area or any subset, whether economic, geographic, or demographic, or individuals with certain health conditions). Another important step is to identify the specific health status and needs of that group and deploy interventions and prevention strategies to improve the health of the group. The interventions target individuals, but they affect the entire population.

The incorporation of technology (e.g., electronic health records) and innovations in health care (e.g., digital home health monitoring) provide the infrastructure to support efforts in successful population health management. A key factor for the success of population health programs is

automation, as managing populations can be highly complex. Technology-enabled solutions are essential to the efficient management of a program.

Let's say a primary care clinic is interested in improving population health for its diabetic patients.

- First, the clinic analyzes the patient registry generated by its electronic health record to identify high-risk type 2 diabetic patients who are not compliant with their medication and who frequently fail to keep their clinic appointments.
- Next, those patients are offered enrollment in a home hemoglobin A1c monitoring program, using a system that digitally records hemoglobin A1c levels taken in the home and then electronically transfers the results to the clinic.
- The system sends an alert to the clinical team when patients' hemoglobin A1c levels are consistently higher than a predetermined threshold.
- A nurse coordinator contacts these patients by phone to help manage medication compliance, answer patient questions, and encourage timely follow-up with clinic visits.
- A nutritionist works with patients to encourage healthy dietary choices, while a social worker addresses any financial constraints to following medical recommendations.

VALUE-BASED CARE

The traditional health care system operates under a **fee-for-service model**, where a fee is collected for each provision of health care service. For example, hospitals and physicians collect a fee each time a patient comes to the hospital for the treatment of congestive heart failure (CHF), including any diagnostic tests or procedures (e.g. chest x-ray, B-type natriuretic peptide, cardiac angiogram).

A new model of health care in the United States is replacing fee-for-service with **value-based care**, where health care professionals are rewarded for keeping entire populations of patients healthy.

Using the CHF example, a value-based system would reward health care professionals for encouraging lifestyle changes that prevent hospital admissions for CHF, such as promoting a heart healthy diet, monitoring home fluid intake, and motivating patients to engage in regular exercise. Instead of rewarding exclusively for the treatment of acute medical problems, the new system provides incentives for the health care system to maintain healthy populations, prevent disease, and avoid acute medical problems through the active monitoring and management of chronic disease. **Quality in health care is measured by outcomes achieved**, rather than the *volume* of services delivered.

Note: Value in patient care can be defined as quality of care divided by total cost of care.

Strategies that increase quality and reduce unnecessary costs result in improved value for patients. Unnecessary costs may be generated from the following examples:

- Duplication of services (e.g., a surgeon orders a routine pre-operative ECG for a patient undergoing elective surgery, not realizing the same test was done 1 week ago in the primary care physician's office and was normal)
- Non evidence-based care (e.g., ordering antibiotics for a viral infection)
- Avoidable inefficiencies in care (e.g., a patient returns to the hospital with acute CHF 1 week after being treated for the same condition because he was unaware that a new diuretic had been started in the hospital and was therefore never filled upon discharge)

Failures in preventive health also lead to avoidable health care spending, as in hospitalization for the treatment of acute pneumonia in a patient who did not receive an influenza vaccination. Shifting the focus from volume of care to value of care will improve the overall status of health care in the United States and contain the currently unsustainable costs of care.

It is important **not to confuse value-based care** with **rationing of care**, which seeks to reduce needed services in order to preserve resources. Value-based care seeks to reduce **unnecessary** or unwanted waste in care which increases cost without increasing quality of care to the patient.

- Studies, for instance, have shown that performing stress cardiac imaging or advanced non-invasive imaging in patients without symptoms on a serial or scheduled pattern (e.g., every 1–2 years) rarely results in any meaningful change in patient management. This practice may, in fact, lead to unnecessary invasive procedures and excess radiation exposure without any proven impact on patients' outcomes.
  - An exception to this rule would be for patients >5 years after a bypass operation.
- Similarly, using antibiotics for a sore throat or runny nose that is due to a viral infection not only provides no immediate benefit to the patient, it may also increase harm from adverse drug reactions or development of antibiotic resistant bacterial strains.

Many health care organizations are developing guidelines and recommendations to promote value-based care. These approaches motivate both patients and clinicians to follow effective care practices; the result is greater value and effectiveness of health care utilization. For example, Choosing Wisely™ (choosingwisely.org) is a national initiative of the American Board of Internal Medicine Foundation, which promotes conversations between patients and physicians about unnecessary medical tests/procedures that increase cost without enhancing patient outcomes.

Population health management employs value-based care principles by promoting preventive care, encouraging care patterns that have been proven effective, and reducing waste and unnecessary care.

Value equation in health care:

$$\uparrow \text{value} = \frac{\uparrow \text{quality}}{\downarrow \text{cost}}$$

IMPLEMENTATION OF POPULATION HEALTH MANAGEMENT

The goal of population health management is to keep a patient population as healthy as possible. The components required to achieve this goal include the following:

- Delivery of patient care through multidisciplinary teams
- Coordination of care across care settings
- Increased access to primary care
- Patient education in disease self-management
- Emphasis on health behaviors and lifestyle choices
- Meaningful use of health information technology for data analysis, clinical communication, and outcome measurement

This requires clinicians to identify target populations of patients who may benefit from additional services, such as patients who require reminders for preventative care appointments or patients not meeting management goals. Continual access to patient data and analysis of outcomes is the key to providing proactive, preventive care.

Steps in Population Health Management:

Step 1: Define population

Step 2: Identify care gaps

Step 3: Stratify risks

Step 4: Engage patients

Step 5: Manage care

Step 6: Measure outcomes

Several advances in technology are required to perform effective population health management and accomplish risk stratification; identify gaps in care; achieve patient education, compliance education, and disease state monitoring; ensure general wellness; as well as to implement and assess specific interventions targeted to selected populations.

- The electronic health record can produce integrated, accessible population-wide data systems capable of generating reports that drive effective quality and care management processes.
- Web-based tools designed to educate patients about their condition, promote self-care, and encourage preventative behaviors have been used successfully to reduce hospitalization rates by enabling patients to take charge of their health.
- Telemedicine programs have been implemented to establish remote care in order to facilitate patient outreach, allow patient follow-up after discharge from the hospital, and improve health care in rural populations.
- The automation of processes and programs is essential in order to make population health management feasible, scalable, and sustainable, such as a health IT system that targets patients in greatest need of services, generates alerts to those patients seeking appropriate and timely appointments with clinicians, and alerts clinicians in real-time to patient care needs.

However, technology alone will not be sufficient for population health management; effective **teamwork** in patient care is also important. Effective population health involves establishing multidisciplinary care teams to coordinate care throughout the entire continuum of care. High-performance clinical care teams can manage a greater number of patients and more comprehensively respond to patient care needs compared with individual clinicians working in isolation. Care teams can include physicians, nurses, nurse practitioners, physician assistants, pharmacists, patient navigators, medical assistants, dieticians, physical therapists, social workers, and care managers, and others.

The **patient-centered medical home (PCMH)** is one model used to deliver patient-centered, value-based care, and it plays an important role in population health management. The medical home model emphasizes care coordination and communication beyond episodic care in order to transform primary care. It stresses prevention, early intervention, and close partnerships with patients to tightly manage chronic conditions and maintain health. The PCMH is not necessarily a physical place, but rather an organizational model that delivers the core functions of primary health care. Key principles in this model include:

- Access to a personal physician who leads the care team within a medical practice
- Adoption of a whole-person orientation to providing patient care
- Integrated and coordinated care
- Focus on quality and safety

The medical home is intended to result in more personalized, coordinated, effective, and efficient care. Many of the goals of PCMH directly support efforts in population health.

In 2006, the Massachusetts General Hospital (MGH) worked with the U.S. Centers for Medicare and Medicaid to establish 1 of 6 population health demonstration projects nationwide. During the 3-year demonstration, the MGH implemented strategies to improve health care delivery to its most vulnerable high risk patients—those with multiple health conditions and chronic disease. The hospital system took steps to address the needs of 2,500 of their highest-risk patients.

- Each patient was assigned to a comprehensive care team consisting of a primary care physician, experienced nurse case manager, social worker, and pharmacist.
- A non-clinical community resource specialist was employed to work with the care teams in addressing non-clinical factors influencing health outcomes (for example, if the patient was not able to come to the primary care office for a scheduled visit because of transportation issues, this specialist connected the patient to local transportation resources).

This structure of care allowed clinicians to focus the majority of their time on patients' medical needs. The results revealed a decrease in hospital readmissions by 20%, and a decrease in emergency room visits by 13% for the patients enrolled in the program. Satisfaction was extremely high among both patients and caregivers, and the system was associated with significant cost-savings. This is one example of using population health to increase quality while decreasing costs, thereby increasing value in patient care.

CHAPTER SUMMARY

- Population health management is an important strategy for improving the quality of patient outcomes, containing costs, and promoting health maintenance.
- Successful population health management requires data-driven clinical decision-making, transformations in primary care leadership, meaningful use of health technology, and patient-family engagement.
- Accountable care involves an integrated, proactive approach to improving the value of health in identified patient populations.

High-Yield Topics

- Understanding and managing population risk (e.g., identifying care gaps)
- Care teams coordinating home health between clinic visits as well as during clinic encounters
- Informatics: sharing information seamlessly with EHR and patient portals
- Engaging patients in health maintenance: screening, prevention, and behavioral health
- Measuring outcomes
- Reducing waste in the system (e.g., duplication, non-value added interventions)
- Improving chronic care: keeping patients out of the hospital by optimizing home and outpatient care

KEY DEFINITIONS

- **Care cycle**: array of health services and care settings, which address health promotion, disease prevention, and the diagnosis, treatment, management, and rehabilitation of disease, injury, and disability
- **Clinical care pathway**: integrated, multidisciplinary outline of anticipated care placed in an appropriate timeframe to help patients with a specific condition/set of symptoms move progressively through a clinical experience to positive outcomes
- **Clinical outcome**: end result of a medical intervention, such as survival or improved health
- **Clinical variation**: variation in the utilization of health care services that cannot be explained by variation in patient illness or patient preferences (Wennberg JH 2010)
- **Continuum of care**: concept involving an integrated system of care, which guides and tracks patients over time through a comprehensive array of health services spanning all levels of intensity of care
- **Cost-effectiveness analysis**: analytic tool in which the costs and effects of at least 1 alternative are calculated and presented, as in a ratio of incremental cost to incremental effect; the effects are health outcomes (e.g., cases of disease prevented, years of life gained, or quality-adjusted life years) rather than monetary measures (e.g., cost-benefit analysis) (Gold et al. 1996)

- **Evidenced-based medicine**: applying the best available research results (evidence) when making decisions about health care
  - Health care professionals who perform evidence-based practice use research evidence, along with clinical expertise and patient preferences. Systematic reviews (summaries of health care research results) provide information, which aids in the process of evidence-based practice.
    - For example, a health care provider recommends acetaminophen to treat arthritis pain in a patient who has recently had stomach bleeding. The health care provider makes this recommendation because research shows that acetaminophen is associated with less risk for stomach bleeds than other common pain relievers. The health care provider's recommendation is an example of evidence-based practice.
- **Health**: a state of complete physical, mental, and social well-being, and not merely the absence of disease or infirmity (WHO definition)
- **Health inequity**: those inequalities in health deemed to be unfair or to stem from some form of injustice; the dimensions of being avoidable or unnecessary have often been added to this concept (Kawachi, Subramanian, and Almeida-Filho 2002)
- **Health-related quality of life**: impact of the health aspects of an individual's life on his quality of life or overall well-being (Gold et al. 1996)
- **Intervention**: any type of treatment, preventive care, or test that a person could take or undergo to improve health or to help with a particular problem
  - Health care interventions include drugs (prescription drugs or drugs that can be bought without a prescription), foods, supplements (such as vitamins), vaccinations, screening tests (to rule out a certain disease), exercises (to improve fitness), hospital treatment, and certain kinds of care (such as physical therapy).
- **Life expectancy**: average amount of time a person will live after a certain starting point, such as birth or the diagnosis of a disease
  - The calculation is based on statistical information comparing people with similar characteristics, such as age, gender, ethnicity, and health. In the United States, for example, the life expectancy from birth for men and women combined is 78.1 years. In England, it is 78.7, and in China it is 72.9 years.
- **Patient-centered**: approach to patient care that focuses on the priorities, preferences, and best interests of the patient
  - It is a partnership among practitioners, patients, and their families to ensure that (a) decisions respect patients' wants, needs, and preferences, and (b) patients have the education and support needed to make decisions and participate in their own care.
- **Patient-centered medical home:** care delivery model whereby patient treatment is coordinated through the primary care physician to ensure that the patient receives the necessary care when and where she needs it, in a manner she can understand
  - The goal is to have a centralized setting, which facilitates partnerships between individual patients, their personal physician, and when appropriate, their family. Care is facilitated by registries, information technology, health information exchange, and other means to assure that patients get optimal care.

- **Population**: any group of individuals for whom consideration of health or health care at the level of the group is likely to advance health
- **Population health**: health of a population as measured by health status indicators, and as influenced by social, economic, and physical environments; personal health practices; individual capacity and coping skills; human biology; early childhood development; and health services (Dunn and Hayes 1999)
- **Public health**: activities that a society undertakes to assure the conditions in which people can be healthy; these include organized community efforts to prevent, identify, and counter threats to the health of the public (Turnock 2004)
- **Quality of life**: a broad construct reflecting a subjective or objective judgment concerning all aspects of an individual's existence, including health, economic, political, cultural, environmental, aesthetic, and spiritual aspects (Gold, Stevenson, and Fryback 2002)
- **Quality measure**: clinical quality measures (CQMs) are a mechanism for assessing observations, treatment, processes, experience, and/or outcomes of patient care
  - In other words, CQMs assess "the degree to which a provider competently and safely delivers clinical services that are appropriate for the patient in an optimal timeframe."
- **Registry**: organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves 1 or more predetermined scientific, clinical, or policy purposes
- **Risk factor**: aspect of personal behavior/lifestyle, environmental exposure, or inborn/inherited characteristic that, on the basis of epidemiologic evidence, is known to be associated with health-related condition(s) considered important to prevent (Last 2001)
- **Screening:** using tests or other methods of diagnosis to find out whether a person has a specific disease/condition before it causes any symptoms
  - For many diseases (e.g., cancers), starting treatment earlier leads to better results. The purpose of screening is to find the disease so that treatment can be started as early as possible. For example, a breast exam and mammogram are both screening tests used to find small breast cancers.
- **Social determinant**: proposed or established causal factor in the social environment, which affects health outcomes (e.g., income, education, occupation, class, social support)
- **Target population**: entire service area or any subset, whether economic, geographic, or demographic, or individuals with certain health conditions
- **Upstream determinants**: features of the social environment, such as socioeconomic status and discrimination, that influence individual behavior, disease, and health status

Practice Questions

1. A 59-year-old man with a history of type 2 diabetes is diagnosed with diabetic retinopathy and referred to ophthalmology for additional management. The patient's primary care physician is interested in reducing the number of patients in the practice who develop similar long-term complications from type 2 diabetes mellitus. Which one of the following is the most important next step?

   (A) Develop an intervention to monitor blood glucose levels for all patients in the practice

   (B) Utilize the patient registry to identify high-risk patients comprising the target population

   (C) Train staff in the clinic to identify early signs of retinopathy

   (D) Request to have an ophthalmologist perform fundoscopic exams on all patients in the practice

   (E) Place a sign in the office depicting the dangers of diabetes

Answer: B. One of the first steps in designing a population health management program is to define the target population and identify common risk factors or gaps in care. Ideally, this should be done prior to implementing any intervention, so that it is clear which patients have the greatest need for the intervention and what risk factor(s) the intervention should address.

- Monitoring blood glucose for all patients, even those without diabetes or not at risk for diabetes, may not be a practical use of resources.
- Training staff to identify retinopathy or having an ophthalmologist perform fundoscopic exams will identify patients who already have long-term complications, rather than adjusting behaviors to prevent complications.
- A sign depicting the dangers of diabetes is not a proactive measure, does not optimally engage patients in self-care, and may only help those who are already in the clinic.

2. An 8-year-old boy is brought to the emergency department by his mother after he develops acute shortness of breath and wheezing. The boy appears anxious but is alert and responsive. He is afebrile and responds well to supplemental oxygen and initial respiratory treatment. He has a history of asthma and has presented with similar symptoms 4 times in the past 12 months. The mother smokes 1-2 packs of cigarettes per day while at home with her son. Which of the following addresses an upstream determinant of health amenable to population health management to improve the patient's long-term outcome?

   (A) Rapid use of nebulizer treatments in the emergency department

   (B) Administration of weight adjusted dose of steroid treatment

   (C) Asking the mom to purchase an inhaler to keep at the home

   (D) Parent education on second-hand smoking risk and enrollment in a smoking cessation program

   (E) Prophylactic antibiotics

Answer: D. Educating parents about the risks of second-hand smoke to children—especially one with a history of asthma—and offering parents enrollment in a smoking-cessation program may have a dramatic benefit to the health of the child and help prevent future asthma attacks. Use of nebulizers or steroids in the emergency department may be necessary to treat the acute episode of care; however, will not help prevent future attacks. The use of antibiotics without indications of bacterial infection (e.g., no fever) is not warranted.

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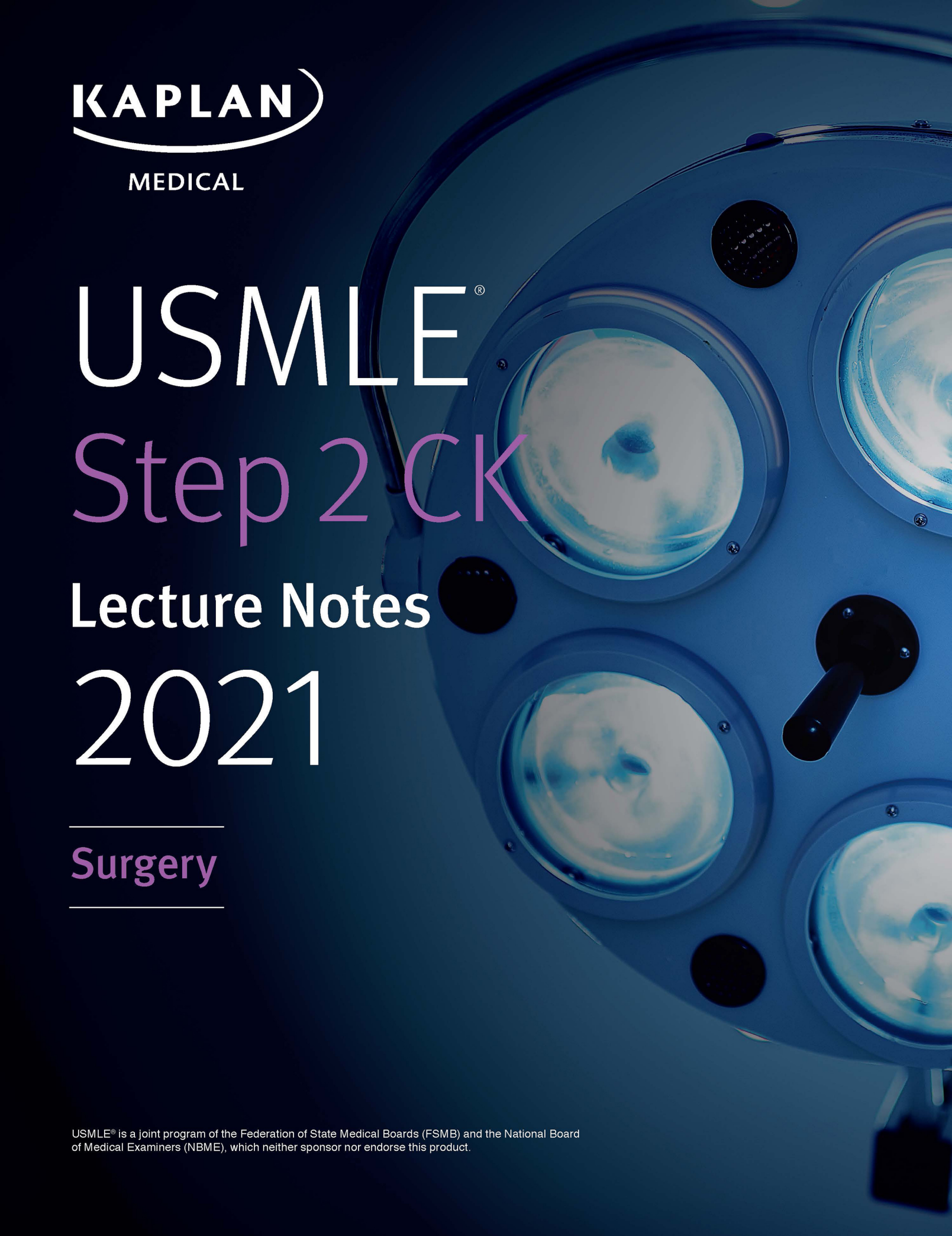

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Preoperative and Postoperative Care 1

Learning Objectives

- ❑ Recognize the factors essential to a preoperative assessment
- ❑ Describe the approach to diagnosis and management of postoperative complications

PREOPERATIVE ASSESSMENT

Prior to **elective** surgery, a patient should be evaluated for potential risks associated with surgery and general anesthesia. These include cardiac, pulmonary, hepatic, nutritional, and metabolic factors that can contribute to intra- and postoperative complications.

Cardiac Risk

The revised cardiac risk index (RCRI) can be used to estimate the risk of cardiac complications for patients undergoing noncardiac operative procedures under general anesthesia. This index is composed of the following variables:

- History of ischemic cardiac disease
- History of congestive heart failure (CHF)
- History of stroke or cerebrovascular accident (CVA)
- Diabetes mellitus
- Chronic kidney disease (CKD, or creatinine >2 mg/dL)
- Planned surgery for thoracic, intra-abdominal, or infrainguinal vascular disease

The risk of cardiac death, cardiac arrest, or nonfatal perioperative myocardial infarction is based on total score.

Score	Risk
0 factors	<0.4% risk
1 factor	0.9% risk
2 factors	6.6% risk
3 or more factors	>11% risk

Note

All general anesthetics **decrease inotropy** and **increase ectopy**.

Pulmonary Risk

Smoking is by far the most common cause of increased pulmonary risk; the problem is compromised ventilation more than compromised oxygenation. Increased pCO_2 and decreased FEV_1 are the most significant predictors of advanced disease.

Smoking history or the presence of chronic obstructive pulmonary disease (COPD) should lead to evaluation with pulmonary function testing.

Smoking cessation and intensive respiratory therapy (physical therapy, expectorants, incentive spirometry, humidified air) should precede elective surgery when possible.

Hepatic Risk

Perioperative risk due to hepatic disease is stratified by several systems, most notably the Child-Pugh classification system and the Model for End-Stage Liver Disease (MELD). The most common disease affecting the liver is alcoholism.

The Child-Pugh system incorporates **A**scites, **B**ilirubin, **C**lotting (prothrombin time), **D**iet (serum albumin), and **E**ncephalopathy (presence/absence). Predicted surgical mortality is as follows:

- Mortality of ~40% is predictable with bilirubin >2 mg/dL, albumin <3 g/dL, prothrombin time >16 sec, or encephalopathy.
- Mortality of ~80–85% is predictable if 3 of the above are present (close to 100% if all 4 exist) or if bilirubin alone is >4 mg/dL, albumin alone is <2 g/dL, or blood ammonia concentration alone is >150 mg/dL.

The MELD score uses the patient's serum bilirubin, creatinine, and INR (normalized prothrombin time) to predict survival and estimate hepatic reserve. Online and app-based calculators are available to calculate the score.

The table shows MELD scores and their associated mortality rates.

MELD score	Mortality rate
<9	1.9%
10–19	6%
20–29	19.6%
30–39	52.6%
≥40	71.3%

Nutritional Risk

Malnutrition results in immunodeficiency and impairs healing, significantly increasing the risk of major surgery. Severe nutritional depletion is identified by one or more of the following:

- Loss of 20% of body weight over 6 months
- Serum albumin <3 g/dL; prealbumin <16 mg/dL
- Serum transferrin level <200 mg/dL

Operative risk is increased significantly in the presence of malnutrition. As few as 4–5 days of preoperative nutritional support (preferably enteral) can make a big difference; 7–10 days is optimal if the surgery can be deferred for that long.

Metabolic Risk

Diabetic ketoacidosis is an absolute contraindication to surgery. Rehydration, return of urinary output, and at least partial correction of the acidosis and hyperglycemia must be achieved before surgery can be undertaken.

Cardiac Risk

> A 72-year-old man with a history of multiple myocardial infarctions is scheduled to have an elective sigmoid resection for diverticular disease. A preoperative echocardiogram shows ejection fraction 35%.

With this ejection fraction, the incidence of perioperative myocardial infarction is ~75%, and the associated mortality rate is 50–90%. In this case, elective surgery is most likely not an option. Continue with medical therapy for the diverticular disease and to optimize cardiac function. If the patient develops an abscess, consider percutaneous drainage to avoid surgical intervention.

> A 72-year-old chronically bedridden man is being considered for emergency cholecystectomy for acute cholecystitis that is not responding to medical management. Four months ago he had a myocardial infarction. Currently he has paroxysmal atrial fibrillation.

This patient has multiple risk factors correlating to a ~20% predicted mortality. Nonsurgical treatment (in this case, percutaneous cholecystostomy tube under local anesthesia) should be pursued.

A 72-year-old man is scheduled to have an elective sigmoid resection for diverticular disease. In the preoperative evaluation it is noted that he has venous jugular distention.

Not a lot of information is provided, but what is given raises suspicion for CHF, which is the worst cardiac risk predictor. Further evaluation starting with echocardiography should be pursued, and the patient should be medically optimized prior to surgery with ACE inhibitors, beta-blockers, and diuretics.

A 61-year-old man with a 20-pack-year smoking history needs elective surgical repair of an abdominal aortic aneurysm. He has cut back on smoking to half a pack per day.

Smoking is by far the most common cause of increased pulmonary risk; smoking cessation and respiratory therapy should precede surgery. Do a complete pulmonary evaluation with pulmonary function testing and optimization with bronchodilators and secretion management. A rapidly growing aneurysm at risk for rupture will need more urgent intervention prior to optimization.

A 49-year-old alcoholic presents with upper gastrointestinal bleeding from a duodenal ulcer. On examination she has bilirubin 3.5 mg/dL, prothrombin time 22 seconds, and serum albumin 2.5 g/dL. Ascites is present.

This patient likely has advanced cirrhosis. Surgical intervention is contraindicated.

- If only one of these conditions is present (bilirubin >2 mg/dL, prothrombin time >16, albumin <3), mortality is predicted at >40%.
- If 3 of these conditions are present, mortality is as high as 85%.

Attempt nonsurgical treatment with blood product resuscitation and consider nonsurgical options such as endoscopic clipping or endovascular embolization.

A 78-year-old man needs palliative surgery for an obstructing cancer of the colon. He has lost 20% of his body weight over the past 2 months. Serum albumin is 2.7.

Any one of these findings indicates severe nutritional depletion. Delaying surgical intervention for several days of preoperative nutrition would decrease some of the risk. This must be taken into consideration when contemplating a palliative procedure.

An older diabetic man presents with a clinical picture of acute cholecystitis that has been present for 3 days. He is profoundly dehydrated and confused, and has blood sugar 550 mg/dL with severe metabolic acidosis.

Diabetic ketoacidosis is a contraindication to surgical intervention. This vignette presents a challenging situation because the patient's hyperglycemia will continue to worsen as long as sepsis is present. Therefore, when the acidosis has resolved, nonsurgical management of the

infection should be pursued—in this case, a percutaneous cholecystostomy tube and definitive source control with cholecystectomy.

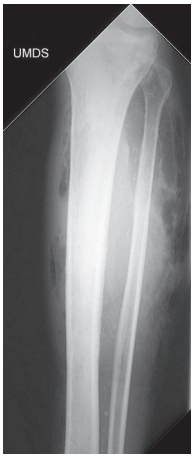
PERIOPERATIVE COMPLICATIONS

Fever

Malignant hyperthermia develops shortly after the onset of the anesthetic (most commonly halothane or succinylcholine). Symptoms include temperature >40 C (104 F), metabolic acidosis, hypercalcemia, and hyperkalemia. A family history may exist; the patient should always be questioned preoperatively. Treatment is **IV dantrolene**, 100% oxygen, correction of the acidosis, and cooling blankets. Monitor postoperatively for the development of myoglobinuria (very uncommon).

Bacteremia is seen within 30–45 minutes of invasive procedures (instrumentation of the urinary tract is a classic example) and presents as chills and a temperature spike as high as 40 C (104 F). Draw multiple sets of blood cultures and start empiric broad-spectrum antibiotics.

Although the condition is rare, severe wound pain and very high fever within hours of surgery should alert you to the possibility of a **necrotizing soft tissue infection**. Immediately remove surgical dressings to examine the wound and promptly return to the OR for wound reopening, debridement, and washout.



Courtesy of SRS-X, Scottish Radiological Society

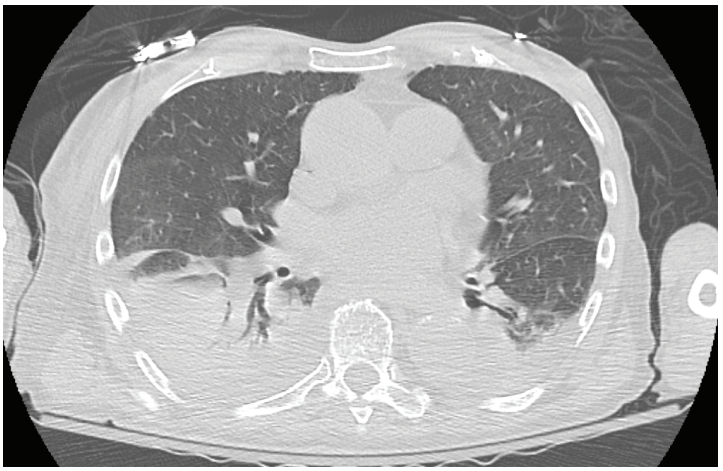
Figure 1-1. Necrotizing Soft Tissue Infection due to *Clostridium Perfringens*

Postoperative fever typically is not as high as in the previous examples, usually 38.3–39.4 C (101–103 F). Fever in the postoperative period is caused (in order of time sequence) by atelectasis, pneumonia, urinary tract infection (UTI), deep vein thrombosis (DVT), wound infection, or deep abscesses.

Atelectasis is the most common source of fever on the first postoperative day. Assess the risk of the other causes already noted, listen to the lungs, do a chest x-ray, and improve ventilation (deep breathing and coughing, postural drainage, incentive spirometry). No need to order a CT or blood cultures in this early postoperative period, as this is generally an empiric diagnosis. Bronchoscopy with clearing of secretions is occasionally necessary.

Clinical Pearl

In post-op patients, fever commonly arises from **W**ind (atelectasis), **W**ater (UTI), and **W**ound (wound infection). (Note that **W**alking [DVT]—historically part of the 4 Ws—is now much less common in the post-op period due to the absolute necessity of DVT prophylaxis.)



Courtesy of Gary Schwartz, MD

Figure 1-2. Atelectasis

Pneumonia will happen in about 3 days if atelectasis is not resolved (atelectasis is a prelude to pneumonia). Fever will persist, leukocytosis will be present, and chest x-ray will demonstrate infiltrate(s). There may be purulent sputum. Obtain sputum cultures and treat with appropriate antibiotics.

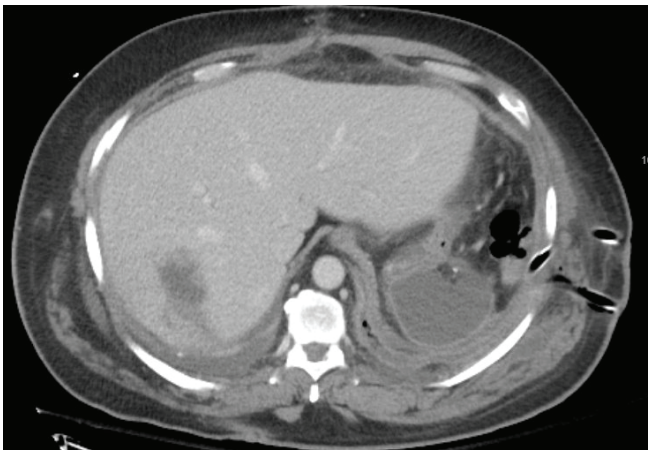
UTI typically produces fever starting on postoperative day 3. Work up with a urinalysis and urinary cultures and treat with appropriate antibiotics. The most common cause is instrumentation (catheterization).

Deep vein thrombosis can result in fever starting around postoperative day 5. Diagnosis requires a high index of suspicion. Physical exam is not very sensitive; U/S is diagnostic. Treatment is systemic anticoagulation, initially with heparin or unfractionated low molecular weight heparin and then transitioned to a long-term anticoagulant. Prophylaxis is mandatory in all surgical patients with early ambulation, compression devices, and/or chemical prophylaxis with low-dose heparin.

Wound infection typically begins to produce fever around postoperative day 7. Physical exam will reveal erythema, warmth, tenderness, and fluctuance. The 7-day delay is because it takes that long from **colonization to infection** (a numbers game).

- If only cellulitis is present, treat with antibiotics.
- If an abscess is present or suspected (most important physical finding is **fluctuance**), the wound must be opened and drained.
- If the case is unclear, use U/S or CT to diagnose.

A **deep abscess** (e.g., intraperitoneal: subphrenic, pelvic, or subhepatic) will start to produce fever around postoperative days 10–15. CT of the appropriate body cavity is diagnostic. Percutaneous image-guided drainage is therapeutic.



Courtesy of Gary Schwartz, MD

Figure 1-3. CT Splenic Bed Abscess

Shortly after the onset of a general anesthetic with inhaled halothane and muscle relaxation with succinylcholine, a patient develops a rapid rise in body temperature, exceeding 40 C (104 F). Metabolic acidosis and hypercalcemia are also noted. A family member died under general anesthesia several years earlier.

This is a classic case of malignant hyperthermia. The history should have been a warning, but once the problem develops, discontinue the anesthetic gas, treat with IV dantrolene, and take the essential support measures:

- 100% oxygen
- Correction of the acidosis
- Cooling blankets

Monitor for myoglobinuria and an acute kidney injury.

Forty-five minutes after completion of a cystoscopy, a patient develops chills and a fever spike to 40 C (104 F).

This is early on after an invasive procedure, and a fever this high means bacteremia. Take blood cultures and start broad-spectrum, empiric IV antibiotic therapy.

On postoperative day 1 after a right hemicolectomy, a patient develops a fever of 38.9 C (102 F).

Fever on day 1 is most commonly due to atelectasis, but all the other potential sources have to be ruled out. Examine the wound and IV sites and take a chest x-ray. Inquire about urinary tract symptoms. Improve the patient's ventilation: deep breathing and coughing, postural drainage, and incentive spirometry. This is all referred to as "pulmonary toilet."

On postoperative day 1 after an abdominal procedure, a patient develops a fever of 38.9 C (102 F). The patient is not compliant with treatment for atelectasis and by postoperative day 3 still has daily fever in the same range.

Bacterial pneumonia has mostly likely developed in the atelectatic lung. Chest x-ray, sputum cultures, and appropriate antibiotics are needed.

A patient who had a right colectomy for colon cancer is afebrile during the first 2 postoperative days, but on day 3 she has a fever spike to 39.4 C (103 F).

A patient who had a right colectomy for colon cancer is afebrile during the first 4 postoperative days, but on day 5 he has a fever spike to 39.4 C (103 F).

A patient who had a right colectomy for colon cancer is afebrile during the first 6 postoperative days, but on day 7 she has a fever spike to 39.4 C (103 F).

Every potential source of post-op fever always has to be investigated, but the timing of the first febrile episode gives a clue as to the most likely source. Remember the "4 Ws": UTI, thromboembolism (now less common because of mandatory prophylaxis), and wound infection are the likely culprits in these vignettes. Urinalysis and urinary culture, lower extremity venous U/S, and physical examination are the respective tests.

A patient who had major abdominal surgery has a normal postoperative course, with no significant episodes of fever until day 10, when his temperature begins to spike up to 39.4 C (103 F) daily.

At this postoperative stage, a deep abscess is the most likely source. CT is diagnostic, and treatment typically is percutaneous drainage.

Chest Pain

Perioperative myocardial infarction (MI) may occur during the operation (most commonly triggered by hypotension), in which case it is detected by the EKG monitor (ST elevation or depression, T-wave flattening). When it happens postoperatively, MI typically presents with chest pain in the first 2–3 days. The most reliable diagnostic test is serum troponin I level. Mortality is 50–90%, greatly exceeding that of MI not associated with surgery. Treatment is directed at the complications. Emergency coronary angiography with percutaneous intervention (angioplasty, stenting) may be lifesaving.

On postoperative day 2 after an abdominoperineal resection for rectal cancer, a 72-year-old man complains of severe retrosternal pain radiating to the left arm. He is short of breath and tachycardic.

During an abdominoperineal resection for rectal cancer, the patient unexpectedly has severe bleeding and is hypotensive on and off for almost 1 hour. The anesthesiologist notes ST depression and T-wave flattening in the EKG monitor.

Perioperative MI happens intraoperatively or within the first 3 days, and the biggest triggering cause is hypovolemic shock and hypotension. The 2 vignettes presented here are typical scenarios, although in practice the classic chest pain picture is often obscured by other ongoing events. Check a 12-lead EKG and serum troponin levels, and contact cardiology.

Pulmonary Embolism

Pulmonary embolism (PE) typically occurs around postoperative day 7 but can occur at any time postoperatively. Elderly patients and those with cancer are at increased risk; postoperative immobilization alone increases the risk. Typical presentation is sudden-onset pleuritic pain accompanied by shortness of breath.

Look for a patient who is anxious, diaphoretic, and tachycardic, with prominent distended veins in the neck and forehead. (Note that a low central venous pressure [CVP] virtually excludes the diagnosis.) Arterial blood gases demonstrate hypoxemia and often hypocapnia due to tachypnea.

CT angiogram (the gold standard) is used for diagnosis. This diagnostic test is a spiral CT with a large IV contrast bolus timed to pulmonary artery filling. **This diagnostic test is not to be delayed.**

Treatment is systemic anticoagulation, initially with heparin, and should be started immediately following diagnosis.

- In decompensating patients with a high index of suspicion, consider starting treatment even before confirming the diagnosis.
- If a PE recurs while the patient is anticoagulated or if anticoagulation is contraindicated, place an inferior vena cava filter to prevent further embolization from lower extremity deep venous thromboses.

Prevention of thromboembolism will also prevent PE.

- Use a sequential compression device on anyone who does not have a lower extremity fracture or significant lower extremity arterial insufficiency.
- In moderate- or high-risk patients, prophylactic anticoagulation is indicated with low-dose heparin (typically 5,000 units subcutaneously/8–12 hours until mobile) or enoxaparin (30–40 mg/24 hours, based on renal function). This is referred to as **chemoprophylaxis**.
- Risk factors for DVT include age >40, pelvic/leg fracture, venous injury, femoral venous catheter, presence of cancer, and anticipated prolonged immobilization.

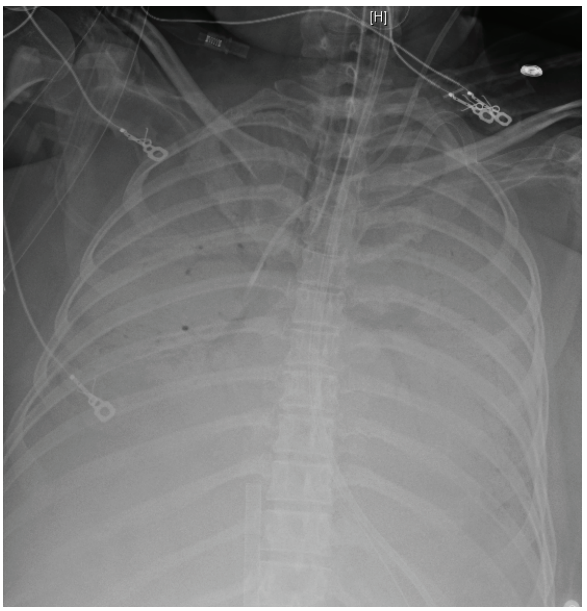
On postoperative day 7 after a broken hip is pinned, a 76-year-old man suddenly develops severe pleuritic chest pain and shortness of breath. When examined, he is found to be anxious, diaphoretic, and tachycardic. He has prominent distended veins in his neck and forehead.

Chest pain this late post-op is most likely due to a pulmonary embolus (PE). This patient is obviously at high risk, and the findings are classic. Arterial blood gas or pulse oximetry is the first test, and hypoxemia and hypocapnia are the expected findings; in their absence, it is not a PE. CT angiogram is the immediate gold standard diagnostic test of choice. Therapy starts with systemic heparinization. Fibrinolysis with tissue plasminogen activator (tPA), either systemic or catheter-directed, is indicated for extreme cases with hemodynamic compromise, as well as consideration of surgical embolectomy. If a PE recurs despite anticoagulation, an inferior vena cava filter is indicated.

Other Pulmonary Complications

Aspiration is a distinct hazard when intubating patients with a full stomach. It can be lethal right away, but more commonly causes a chemical injury of the tracheobronchial tree—pneumonitis—that can progress to pneumonia and respiratory failure. Prevention includes strict restriction of oral intake prior to surgery and antacids before induction. Therapy starts with bronchoscopic lavage and removal of acid and particulate matter, followed by bronchodilators and respiratory support. Steroids have not been demonstrated to improve outcomes and therefore are not usually indicated. Antibiotics are indicated only where there is evidence of the resultant pneumonia—e.g., leukocytosis, sputum production and culture, and focal consolidation on chest x-ray. This typically does not present for several days following the insult.

Adult respiratory distress syndrome (ARDS) is seen in patients with a complicated post-op course, often with sepsis as the precipitating event. These patients demonstrate bilateral pulmonary infiltrates and hypoxia with no evidence of CHF. The centerpiece of therapy is positive end-expiratory pressure (PEEP) with low volume ventilation. (Excessive ventilatory volumes have been demonstrated to result in barotrauma.) A source of sepsis must be sought and corrected.



Courtesy of Gary Schwartz, MD

Figure 1-4. ARDS

Intraoperative tension pneumothorax can develop in patients with traumatized or emphysematous lungs who are subjected to positive-pressure breathing. They become progressively more difficult to ventilate, with rising airway pressure, steadily declining BP, and steadily rising CVP.

- If the abdomen is open, quick decompression can be achieved through the diaphragm (but the risk is contamination of the pleural cavity).
- Alternatively (and better), needle decompression in the midclavicular line followed by formal chest tube is indicated.

> An awake intubation is being attempted in a drunk and combative man who has sustained a gunshot wound to the abdomen. In the struggle, the patient vomits and aspirates a large amount of gastric contents with particulate matter.

This is every anesthesiologist's nightmare. Aspiration results in a chemical injury to the tracheobronchial tree ("aspiration pneumonitis"). This is an inflammatory problem, not an infectious process, so antibiotics are not immediately indicated. However, the irritation results in pulmonary failure and increases the risk of secondary pneumonia. Prevention is best: empty stomach, antacids before induction, rapid sequence induction with manual cricoid pressure. Once aspiration happens, however, bronchoscopic lavage and removal of particulate matter are the first steps, followed by bronchodilators and respiratory support. Steroids are usually not helpful.

> In week 2 of a complicated postoperative period, a young patient with multiple gunshot wounds to the abdomen becomes progressively disoriented and unresponsive. The patient has bilateral pulmonary infiltrates and PaO_2 of 65 mm Hg while breathing 40% oxygen.

The reason for the mental changes is obvious: the patient is not getting enough oxygen in the blood. The rest of the findings, however, specifically identify ARDS. The centerpiece of therapy for ARDS is mechanical ventilation with high PEEP and low tidal volumes. Also consider why this has developed now: in an older patient with preexisting lung disease, an acute illness can exacerbate the problem; in a patient with normal lungs, chest trauma and sepsis are the most common etiologies.

> A trauma patient is undergoing a laparotomy for a seatbelt injury. She also sustained several broken ribs. Halfway through the case it becomes progressively difficult to ventilate the patient, and oxygen saturation and blood pressure steadily decline. There is no evidence of intra-abdominal bleeding.

This patient has an intraoperative tension pneumothorax. Likely, while the patient was receiving positive-pressure ventilation, one of the broken ribs punctured the lung. The best approach is immediate transdiaphragmatic decompression, or better, transthoracic needle decompression followed by formal chest tube placement.

Disorientation/Coma

When a postoperative patient becomes confused and disoriented, **hypoxia** is the first concern and **sepsis** is a close second. If airway protection is threatened, check an arterial blood gas and provide respiratory support.

Delirium tremens (DTs) is very common in the alcoholic whose drinking is suddenly interrupted by hospital admission. During postoperative day 2 or 3, the patient gets confused, has hallucinations, and becomes combative. IV benzodiazepines are the standard therapy, but oral alcohol is sometimes available at hospitals for this indication (not frequently given in today's environment). DTs must be recognized and treated: it can be fatal!

Electrolyte imbalances, particularly alterations in sodium concentration, can have a profound effect on a patient's mental status. Both hypernatremia and hyponatremia can produce confusion, seizures, lethargy, and coma.

Ammonium intoxication is a common source of coma in the cirrhotic patient. In patients with cirrhosis, inability to detoxify absorbed protein from GI bleeding can produce "hepatic coma"; this effect may also be seen after implementation of a portosystemic shunt (e.g., TIPS procedure).

> Eighteen hours after abdominal aortic aneurysm repair, a patient becomes disoriented.

This is a very brief vignette, but of the long list of things that can produce post-op disorientation, the most lethal one if not promptly recognized and treated is hypoxia. Physical examination and vital signs will likely indicate hypoxemia; obtain an arterial blood gas if unsure or to quantify. Alternative etiologies are mostly metabolic: uremia, hyponatremia, hypernatremia, ammonium, hyperglycemia, DTs, or medications.

> A recovered alcoholic undergoes an elective colon resection for recurrent diverticular bleeding. The patient reports that he has not touched a drop of alcohol for the past 6 months. On postoperative day 3 he becomes disoriented and combative, and claims to see elephants crawling up the walls. The spouse then reveals that the patient actually drank heavily up until the day of hospital admission.

This case clearly describes DTs. The standard management relies on benzodiazepines. Some hospitals allow oral intake of alcohol, but that is less common these days.

> Twelve hours after completion of an abdominal hysterectomy, a 42-year-old woman becomes confused and lethargic, complains of severe headache, has a grand mal seizure, and finally goes into a coma. Review of the chart reveals that an order for D5W, to run in at 125 mL/h, was mistakenly implemented as 525 mL/h.

This is a classic example of water intoxication. A very low serum sodium concentration will confirm it. Mortality for this iatrogenic condition is very high, and therapy is quite controversial. Very careful use of hypertonic saline (3%) is a reasonable answer in this extreme scenario. Indications are generally coma or seizures.

> Eight hours after completion of a transsphenoidal hypophysectomy for prolactinoma, a young woman becomes lethargic, confused, and eventually comatose. Review of the record shows that her urinary output since surgery has averaged 600 mL/h, although her IV fluids are going in at 100 mL/h.

This case illustrates the reverse of the previous vignette: large, rapid, unreplaced water loss from surgically induced diabetes insipidus. The labs will show significant hypernatremia. The safest therapy is an infusion of 1/3 or 1/4 normal saline to replace the lost fluid; in this acute setting, D5W would be acceptable.

> A cirrhotic patient goes into coma after receiving an emergency portocaval shunt for bleeding esophageal varices.

This clinical case is brief but unmistakable: the culprit here will be ammonia. If the case also involves hypokalemic alkalosis and high cardiac output combined with low peripheral resistance, overt liver failure has occurred.

Urinary Complications

Postoperative urinary retention is extremely common, particularly after surgery in the lower abdomen, pelvis, perineum, or groin. The patient feels the need to void but cannot. Bladder scanning and catheterization should be performed 6–8 hours postoperatively if no spontaneous voiding has occurred. Indwelling Foley catheter placement is indicated at the second consecutive catheterization.

Zero urinary output typically is caused by a mechanical problem (not a biologic one), as even patients with renal failure will have some output. Look for a plugged or kinked catheter, and flush the tubing to dislodge any clot that may have formed. You need to know this, but likely the nurse will irrigate and replace the catheter if blocked without your definitive order.

Low urinary output (<0.5 mL/kg/hr) in the presence of **normal BP** (i.e., not because of shock) represents either fluid deficit or an acute kidney injury. Always check the BP, as hypotension will cause this (renal blood flow follows cardiac output). The treatment is fluids, not diuretics.

- A low-tech diagnostic test is a fluid challenge: a bolus of 500 mL of IV fluids infused over 10–20 minutes. Patients who are dehydrated will respond with a temporary increase in urinary output; those in renal failure will not.
- A more scientific test is to measure urinary sodium: it will be <10 or 20 mEq/L in the dehydrated patient with normally functioning kidneys; it will exceed 40 mEq/L in cases of renal failure.
- An even more scientific test is to calculate the fractional excretion of sodium, or FeNa. This involves measuring plasma and urinary sodium and creatinine. In acute kidney injury, the ratio >2; in hypovolemia it is <1.

> Six hours after undergoing a hemorrhoidectomy under spinal anesthesia, a 62-year-old man complains of suprapubic discomfort and fullness. He feels the need to void but has been unable to do so since the operation. There is a palpable suprapubic mass that is dull to percussion. Bladder scanning reveals a significant volume of urine.

By far the most common urinary problem post-op is the inability to void, and men are more commonly affected. Treatment is in-and-out bladder catheterization. If bladder catheterization has to be repeated again after another 6–8 hours, a Foley catheter should be left in place for 24–48 hours before removal is attempted.

> A man has had an abdominoperineal resection for cancer of the rectum, and an indwelling Foley catheter was left in place after surgery. The nurses are concerned because even though the patient's vital signs have been stable, urinary output in the last 2 hours has been zero.

In the presence of renal perfusing pressure, urinary output of zero invariably means a mechanical problem: the catheter is plugged or kinked. More ominous possibilities include injury of both ureters or thrombosis of the renal vessels, but these causes are much more rare.

> Several hours after completion of multiple surgery for blunt trauma in an average-sized adult, the patient's urinary output in 3 consecutive hours is reported as 12 mL/h, 17 mL/h, and 9 mL/h. Blood pressure has hovered around 95–130 mm Hg systolic during that time.

The patient's kidneys are perfusing, but she is either behind in fluid replacement or has gone into renal failure. A fluid challenge would suggest which situation exists: a bolus of 500 mL given over 10–20 minutes should produce diuresis in the dehydrated patient but will not do so in renal failure.

The more precise technique—and the preferred exam answer—is to measure urinary sodium (<10–20 mEq/L in dehydration, >40 mEq/L in renal failure). An even more elegant calculation is measurement of FeNa (<2 in renal failure).

Abdominal Distention

Paralytic ileus is to be expected in the first few days after abdominal surgery. Presentation includes:

- Bowel sounds: absent or hypoactive
- No passage of gas
- Mild distention (some cases)
- **No pain**

The condition is prolonged by electrolyte abnormalities, especially hypokalemia and hypomagnesemia. Be patient, as it will usually resolve with time.

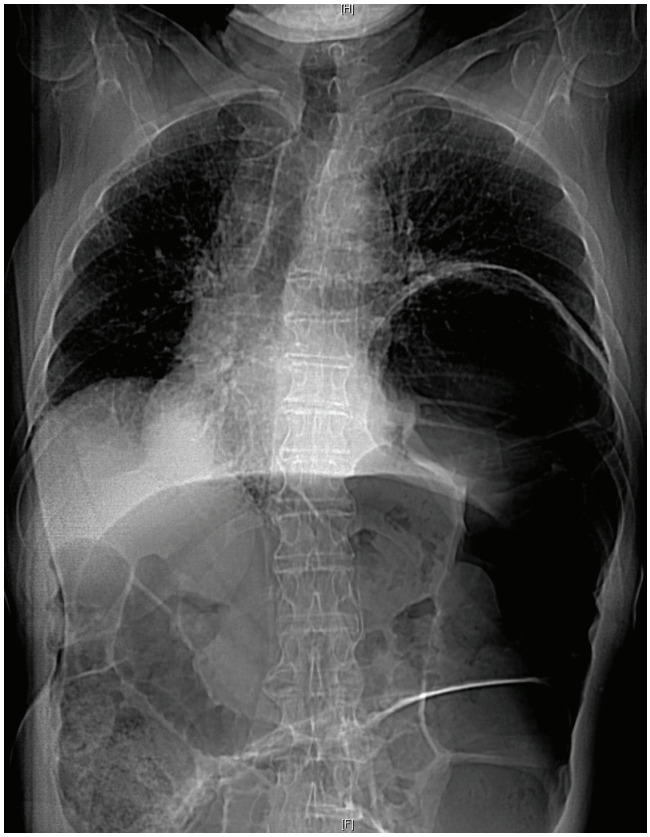
Early mechanical bowel obstruction can happen during the postoperative period because of adhesions. Apparent paralytic ileus that fails to resolve after 5–7 days is most likely an early mechanical bowel obstruction. X-ray will show dilated loops of small bowel and air-fluid levels.

Diagnosis is confirmed with an abdominal CT that demonstrates a transition point between proximal dilated bowel and distal collapsed bowel at the site of the obstruction. Surgical intervention is needed to correct the problem. Remember that with bowel obstruction, **there is pain**.

Ogilvie syndrome (or pseudo-obstruction) is a poorly understood but very common condition that could be described as a paralytic ileus of the colon.

- A functional (physiologic) obstruction, not mechanical obstruction
- Classically seen in elderly, sedentary patients (Alzheimer's, nursing home residents) who have become further immobilized owing to either surgery (broken hip, prostatic surgery) or anticholinergic or psychotropic medications
- Symptoms include abdominal distention without tenderness
- X-ray shows a massively dilated colon
- Treatment
  - Fluid and electrolyte correction first
  - Then, mechanical obstruction must be ruled out radiologically
  - Endoscopy (diagnostic and therapeutic) may include leaving a rectal tube in place
  - IV neostigmine to restore colonic motility, but given the risk of significant bradycardia, can be done only during continuous telemetric monitoring

If this syndrome is not treated, the cecum is the usual point of rupture (law of Laplace).



Courtesy of Gary Schwartz, MD

Figure 1-5. X-Ray Dilated Colon

> Four days after exploratory laparotomy for blunt abdominal trauma with resection and anastomosis of damaged small bowel, a patient has abdominal distention without abdominal pain. She has no bowel sounds and has not passed flatus, and abdominal x-ray shows dilated loops of small bowel without air-fluid levels.

This case is likely a postoperative paralytic ileus, which can be expected under the circumstances. NPO and NG suction should be continued until peristaltic activity resumes. If it does not, CT of the abdomen should be taken to rule out a mechanical obstruction, visible as a transition point between the proximal dilated bowel and the distal collapsed bowel at the site of obstruction. Hypokalemia should also be ruled out. A technical error at the anastomosis site should always be considered. Be patient!

> An 80-year-old man with Alzheimer's disease living in a nursing home undergoes surgery to repair a fractured femoral neck. On postoperative day 5 the patient's abdomen is noted to be grossly distended and tense, but nontender. He has occasional bowel sounds. X-ray shows a very distended colon and a few distended loops of small bowel.

In the elderly, who are not very active to begin with and are now further immobilized, massive colonic dilatation (Ogilvie syndrome) is commonly seen. Correct the fluids and electrolytes first. Neostigmine can dramatically improve colon motility at the cost of **very significant side effects**. Colonoscopy is the most successful treatment should intervention become indicated.

Wound Infections

Wound infections are typically seen around postoperative day 7. Manage with IV antibiotics and, potentially, by reopening the wound partially or completely to allow for drainage.

Wound dehiscence is typically seen around postoperative day 5 after open laparotomy. The wound may look intact, but a **large volume** of pink ("salmon-colored") fluid is noted to be soaking the dressing; this is peritoneal fluid draining through a dehiscence in the fascial closure. Reoperation is indicated to avoid evisceration and peritonitis. In high-risk patients, nonsurgical management with negative pressure wound therapy may suffice.

Evisceration is a catastrophic complication of wound dehiscence where the fascia closure opens and the abdominal contents herniate. It typically happens when the patient (who may not have been recognized as having a dehiscence) coughs, strains, or gets out of bed. The patient must be kept in bed and the bowel covered with large sterile dressings soaked with warm saline. Emergency abdominal closure is mandatory.

Enterocutaneous fistula is a devastating complication that develops between the gastrointestinal tract and the skin, typically through a surgical wound or drain site.

- If the enterocutaneous fistula does not empty completely to the outside ("uncontrolled") but instead leaks into a body cavity, it may precipitate an abscess and lead to sepsis; treatment is complete drainage.
- If it drains freely ("controlled"), sepsis does not usually develop, but fluid and electrolyte loss, nutritional depletion, and erosion of the abdominal wall are potential problems.

Complications associated with GI fistulas depend on the location and volume of the fistula:

- Less problematic in the distal colon
- Present but manageable in low-volume fistula (up to 200–300 mL/day)
- Daunting in high-volume fistulas (several liters per day) arising from upper GI tract

Fluid and electrolyte replacement, nutritional support, and protection of the skin of the abdominal wall are done to keep the patient alive until nature heals the fistula.

Fistulas are a nightmare to both the patients and surgeons, as the healing of even a controlled fistula can take weeks or months.

> On postoperative day 5 after a laparotomy, it is noted that large amounts of salmon-colored clear fluid are soaking the patient's dressings.

This is the classic presentation of a wound dehiscence. Surgical exploration is indicated, with reclosure of the fascia. In a very high-risk patient, consider nonsurgical management with negative pressure wound therapy.

> Nurses report that on postoperative day 5 after a laparotomy, a patient is draining clear pink fluid from his abdominal wound. A medical student removes the dressing and asks the patient to sit up so he can be helped out of bed to the treatment room. When he complies, the wound opens wide and small bowel rushes out.

This variant describes evisceration, a serious problem. Put the patient back in bed, cover the bowel with large, moist dressings soaked in warm saline (moist and warm are the key), and then get him to the OR for reclosure.

> A patient presents to the surgeon's office postoperative day 7 after an open appendectomy. The incision is noted to be red, hot, tender, and fluctuant. She reports fever for the past 2 days.

If there were just a bit of redness, or symptoms occurred earlier in the postoperative course, this could be a case of superficial cellulitis and managed with antibiotics alone. However, this far post-op and with the physical examination findings, this scenario describes a postoperative wound infection. There is likely to be pus; the wound must be opened to allow for drainage, and antibiotics must be administered. If there is doubt as to the presence or absence of a drainable collection, U/S is diagnostic.

> Nine days after a patient undergoes sigmoid resection for cancer, the wound drains a brown fluid that is clearly feculent. The patient is afebrile and otherwise doing quite well.

This scenario describes a fecal fistula. If draining to the outside, it is unruly and inconvenient but not life-threatening. The fistula will close eventually with little or no therapy if there are no limiting factors (FRIENDS mnemonic). If feces were accumulating on the inside ("uncon-

Note

Natural wound healing will take place unless the following **FRIENDS** (mnemonic) are present:

- **F**oreign body
- **R**adiation injury
- **I**nfection or **I**BD
- **E**pithelialization
- **N**eoplasm
- **D**istal obstruction
- **S**teroid use

trolled"), the patient would be febrile and sick and would need drainage and probably a diverting colostomy.

> Eight days after a difficult hemigastrectomy and gastroduodenostomy for gastric ulcer, a patient begins to leak 2–3 L of green fluid per day through the right corner of her bilateral subcostal abdominal wound.

A patient who is febrile and sick, with an acute abdomen, needs to be explored for what is likely an uncontrolled fistula. However, if all the gastric and duodenal contents are leaking to the outside ("controlled"), further immediate surgery can often be avoided:

- Provide fluid/electrolyte replacement
- Deliver elemental nutritional support into the upper jejunum
- Provide local wound care to prevent skin breakdown
- Consider somatostatin or octreotide to diminish the volume of GI fluid loss

Total parenteral nutrition (TPN) is second choice, but it is less effective and carries greater potential risk of bloodstream infections.

Fluid and Electrolyte Imbalance

Hypernatremia means that the patient has lost water (or other hypotonic fluids) and become dehydrated. The condition typically presents as alterations in neurologic function; the extent of brain dysfunction depends on the magnitude and time frame over which the hypernatremia developed. Every 3 mEq/L that serum sodium concentration exceeds 140 represents approximately 1 L of water lost.

- If the problem develops slowly (i.e., over several days), the brain will adapt, and the only clinical manifestations will be those of volume depletion.
- If the problem happens rapidly (e.g., osmotic diuresis, diabetes insipidus), the brain will not be able to adapt, and thus more profound CNS symptoms will develop.

Treatment is volume repletion to correct overall volume rapidly (hours), while tonicity is corrected slowly (days). This is achieved by using 5% dextrose in half-normal saline rather than D5W.

Hyponatremia means the patient has retained a net excess of water and hypotonicity has developed. There are 2 potential scenarios:

- A patient who is losing large amounts of isotonic fluids (typically from the GI tract) is forced to retain water if she has not received appropriate replacement with isotonic fluids. Volume restoration with isotonic fluids (NS or lactated Ringer's [LR]) will correct the hypovolemia and allow the body to unload the retained water slowly and safely and return the tonicity to normal.
- A patient who starts with normal fluid volume adds to it by retaining water in the presence of inappropriate amounts of antidiuretic hormone (ADH) (e.g., post-op water intoxication or inappropriate ADH secreted by tumors). Rapidly developing hyponatremia (water intoxication) produces CNS symptoms because the brain has not had time to adapt; it requires careful use of hypertonic saline (3 or 5%). In hyponatremia that develops slowly in response to inappropriate ADH, the brain has time to adapt; therapy should be water restriction.

Hypokalemia develops slowly, over days, when potassium is lost from the GI tract (all GI fluids have lots of potassium) or in the urine (because of loop diuretics or excess aldosterone) and is not replaced. Hypokalemia develops rapidly, over hours, when potassium moves into the cells—for example, when diabetic ketoacidosis is corrected. Treatment is IV potassium replacement at a rate not faster than 10 mEq/hr.

Hyperkalemia will develop slowly if the kidney cannot excrete potassium (renal failure, aldosterone antagonists), or rapidly if potassium is being released from cells into the blood (crushing injuries, dead tissue, acidosis).

Treatment must take into account whether the kidneys are functioning. Emergent management includes stabilizing cellular membranes with IV calcium and "pushing potassium into the cells" through the use of IV glucose and insulin. Loop diuretics excrete potassium in the urine (if the kidneys are working), and sodium polystyrene sulfonate (oral or rectal) may absorb potassium via the GI tract. Dialysis may be needed in the event of renal failure.

Metabolic acidosis can result from any of the following:

- Excessive production of fixed acids (diabetic ketoacidosis, lactic acidosis, low-flow states)
- Inability of the kidney to eliminate fixed acids (renal failure)
- Loss of buffers (loss of bicarbonate-rich fluids from GI tract)

In all cases, blood pH is low (<7.4), serum bicarbonate is low (<22), and there is a base deficit. When abnormal acids are piling up in the blood, there is also an "anion gap" in which serum sodium exceeds the sum of chloride and bicarbonate by >10 or 15. The anion gap does not exist when the problem is loss of buffers. This can be fatal, as metabolic acidosis increases ectopy and decreases inotropy.

Treatment of metabolic acidosis is aimed at treating the underlying cause. Bicarbonate therapy will correct the pH temporarily but can risk producing a "rebound alkalosis." For chronic acidosis, renal loss of K^+ will cause a deficit that does not become obvious until the acidosis is corrected. Be prepared to replace K^+ as part of the treatment.

Metabolic alkalosis classically occurs in scenarios involving loss of acidic gastric fluid, e.g., prolonged emesis or NG suction. It can also develop if excess bicarbonate is administered. Symptoms include low K+, low Cl−, and high bicarbonate (hypokalemic, hypochloremic metabolic alkalosis).

Treatment of metabolic alkalosis is chloride and potassium replacement, thereby allowing the kidneys to correct the problem.

Respiratory acidosis and alkalosis result from impaired ventilation (acidosis) or abnormal hyperventilation (alkalosis). Symptoms include abnormal PCO_2 (low in alkalosis, high in acidosis) and abnormal blood pH. Treatment is correction of the underlying respiratory problem.

Note that metabolic acid-base derangements may be accompanied by respiratory compensatory changes. For example, acute metabolic acidosis will result in tachypnea with lowering of pCO_2 to mitigate the decrease in pH arising from the primary derangement (in this case, metabolic acid).

Remember that metabolic acidosis has the same effects on the heart that general anesthetics have: **decreased inotropy** and **increased ectopy**.

> Eight hours after completion of a transsphenoidal hypophysectomy for a prolactinoma, a young woman becomes lethargic, confused, and eventually comatose. Review of the record shows that her urinary output since surgery has averaged 600 mL/h, while IV fluids are infusing at 100 mL/h. Serum sodium determination shows concentration 152 mEq/L.

Elevated concentration of serum sodium invariably means that the patient has lost pure water (or hypotonic fluids). Every 3 mEq/L above the normal of 140 represents 1 L lost. This woman is 4 L shy, which fits her history of a diuresis of 500 mL/h more than her intake. She should be given 4L of D5W or possibly D5-1/3NS.

> Several friends go on a weekend camping trip in the desert. On day 2 they get lost and aren't rescued until one week later. One patient is brought to your hospital—awake and alert—with obvious clinical signs of dehydration. Serum sodium concentration is 155 mEq/L.

The patient has also lost water, about 5 L, but has done so slowly by pulmonary and cutaneous evaporation over 5 days. He is hypernatremic, but his brain has adapted to the slowly changing situation. Were he to be given 5 L of D5W, the rapid correction of his hypertonicity would be dangerous. Five liters of D5-1/2NS is a much safer plan.

> Twelve hours after undergoing an abdominal hysterectomy, a 42-year-old woman becomes confused and lethargic, complains of severe headache, has a grand mal seizure, and finally goes into coma. Review of the chart reveals that an order for D5W to run in at 125 mL/h was mistakenly implemented as 525 mL/h. Her serum sodium concentration is 122 mEq/L.

In the surgical patient with normal kidneys, hyponatremia invariably means that water (without sodium) has been retained, so the body fluids have been diluted. In this case a lot of IV water was given, and the ADH produced as part of the metabolic response to trauma has held onto it. Rapidly developing hyponatremia (water intoxication) is a big problem, as the brain has no time to adapt; once it has occurred, therapy is controversial. For the sake of the exam, replete with hypertonic saline (3 or 5%) given 100 mL at a time and reassess (clinically and with bloodwork) before each subsequent dose.

> A 62-year-old woman comes in for her scheduled chemotherapy administration for metastatic cancer of the breast. Although she is quite asymptomatic, the lab reports serum sodium concentration of 122 mEq/L.

In this setting, water has also been retained (by ADH produced by the tumor), but so slowly that the brain has kept up with the developing hypotonicity. Rapid correction would be ill-advised at best and lethal at worst. Water restriction, on the other hand, will slowly allow the abnormality to reverse itself.

> A 68-year-old woman comes in with an obvious incarcerated umbilical hernia. She has gross abdominal distention, is clinically dehydrated, and reports persistent fecaloid vomiting for the past 5 days. She is awake and alert. Serum sodium concentration is 118 mEq/L.

Hyponatremia means water retention, but in this case the problem began with loss of isotonic (sodium-containing) fluid from her gut. As the patient's extracellular fluid became depleted, her body retained whatever water it could: exogenous from oral intake and endogenous from catabolism. Consequently, she is now simultaneously volume-depleted and hyponatremic (hypotonic).

This patient desperately needs volume replacement, but it must not be corrected too quickly. Administer isotonic fluids in quantity: Start with 1 or 2 L/h of normal saline or Ringer's lactate, depending on the acid-base status (use clinical variables to fine tune the rate). Once fluid volume is replenished, the patient's body will unload the retained water and correct its own tonicity.

> A patient with severe diabetic ketoacidosis comes in with profound dehydration and a serum potassium concentration of 5.2 mEq/L. After several hours of vigorous therapy with insulin and IV fluids (saline, without potassium), the patient's serum potassium concentration is 2.9 mEq/L.

Severe acidosis precipitates a loss of potassium in the urine. While the acidosis is present, however, the serum concentration is high because potassium ions have come out of the cells in exchange for hydrogen ions. Once the acidosis is corrected, that potassium rushes back into the cells, and the true magnitude of the potassium loss becomes evident.

The patient obviously needs potassium. Under most circumstances, 10 mEq/h is a safe limit for a peripheral IV line. In extreme settings, 20 mEq/h can be justified, but central venous catheter placement is indicated.

> An 18-year-old woman slips and falls under a bus, and her right leg is crushed. On arrival at the ED she is hypotensive, and she receives several units of blood. Over the next several hours the patient is in and out of hypovolemic shock and develops acidosis. Serum potassium concentration, which was 4.8 mEq/L at the time of admission, is reported at 6.1 a few hours later.

The elevated serum potassium could have multiple etiologies: rhabdomyolysis from the crushed leg, hemolysis from multiple blood transfusions, and/or transcellular migration from acidosis. With low perfusing pressure (in and out of shock), the kidneys have failed to eliminate it.

This patient needs multiple treatment strategies: BP improvement to allow for urinary clearance, intracellular transport using D50 and insulin, GI elimination with exchange resins, and an NG tube. If those are not successful, urgent hemodialysis is indicated. During the stabilization period, IV calcium should be administered to stabilize the cellular membrane.

Clinical Pearl

The definitive compensatory mechanism in acid-base balance is the kidney: "**urine follows serum**," i.e., if acidotic, the kidney will excrete acid (retain bicarb), and vice versa.

An elderly man with alcoholism, diabetes, and marginal renal function sustains multiple traumas while driving under the influence of alcohol. In the course of his resuscitation and multiple surgeries, he is in and out of shock for prolonged periods of time. Blood gases show pH 7.1 and PCO_2 32 mm Hg. Serum electrolytes are sodium 138 mEq/L, chloride 98 mEq/L, and bicarbonate 15 mEq/L.

This man has every risk factor for developing metabolic acidosis through retention of fixed acids (rather than by loss of bicarbonate). The driving force in this case is the state of shock, with lactic acid production; the diabetes, alcohol, and bad kidney are also contributing.

Labs confirm metabolic acidosis here (low pH and low bicarbonate). His body is trying to compensate by hyperventilating (low PCO_2), and he exhibits the classic anion gap: the sum of chloride and bicarbonate is 25 mEq/L less than the serum sodium concentration, instead of the normal 10–15 mEq/L.

The classic treatment for metabolic acidosis is bicarbonate or a bicarbonate precursor such as lactate or acetate. However, in a case like this, this tends to result in alkalosis once the low-flow state is corrected. Thus the emphasis here should be on fluid resuscitation with Ringer's lactate. Avoid large volumes of saline, which would deliver too much chloride.

A patient who has undergone a subtotal gastrectomy for cancer with a Billroth II reconstruction develops a blowout of the duodenal stump and, subsequently, a duodenal fistula. For the past 10 days, 750–1,500 mL/day of green fluid has been draining from the incision. Serum electrolytes are sodium 132 mEq/L, chloride 104 mEq/L, and bicarbonate 15 mEq/L. Blood pH is 7.2 and PCO_2 is 35 mm Hg.

This is another case of metabolic acidosis, but with a normal anion gap. The patient has been losing lots of bicarbonate out of the fistula. The problem would not have developed if his IV fluid replacement had contained lots of bicarbonate (or lactate, or acetate). The use of those agents is now indicated.

Clinical Pearl

Pyloric stenosis in children presents with the same electrolyte abnormality as in adults. Treatment for both populations is surgical (pyloromyotomy). In preparation for surgery, children should be resuscitated with only 1/2 NS to avoid hypernatremia, which can be a consequence.

A patient with severe peptic ulcer disease develops pyloric obstruction and has protracted vomiting of clear gastric contents (i.e., without bile) for several days. Serum electrolytes show sodium 134 mEq/L, chloride 82 mEq/L, potassium 2.9 mEq/L, and bicarbonate 34 mEq/L.

This is a classic case of hypochloremic, hypokalemic, metabolic alkalosis secondary to loss of acidic gastric juice. The patient needs to be rehydrated (choose saline rather than Ringer's lactate) and infused with a lot of potassium chloride ($\geq$10 mEq/hr).

Trauma 2

Learning Objectives

- ❑ Describe the algorithm for evaluating a trauma patient
- ❑ Recognize management of burns, bites, and stings

The initial evaluation of a trauma patient requires a systematic approach to identify life-threatening injuries. This involves 2 parts:

- **Primary survey** to evaluate for all potential injuries; necessary interventions are performed during this time
- After the primary survey is complete and the patient is deemed to be stable, **secondary survey** to do a head-to-toe examination and evaluate all organ systems

PRIMARY SURVEY

The primary survey uses a systematic ABCDE approach to assess a rapidly deteriorating patient: **A**irway, **B**reathing, **C**irculation, **D**isability (neurological exam), and **E**xposure. This is also the **order of priority**.

Airway (A)

An airway should be secured before the situation becomes critical. The first step in the evaluation of trauma is airway assessment and protection.

- If the patient is conscious and speaking in a normal tone of voice, the airway is considered intact.
- If the patient has facial or neck trauma, an expanding hematoma or subcutaneous emphysema in the neck, noisy or "gurgly" breathing, or neurologic deficit with Glasgow coma score ≤8, the airway is considered unprotected.

In the field, an airway can be secured via laryngeal mask airway or orotracheal intubation.

In the ED, an airway can be established by orotracheal intubation or cricothyroidotomy. If the use of intubation is precluded or unsuccessful, surgical cricothyroidotomy may be needed.

Clinical Pearl

If an airway is secured via cricothyroidotomy, formal tracheostomy must be performed later to prevent airway stenosis.

Clinical Pearl

In patients age <8, tracheostomy is preferred over cricothyroidotomy, which can cause airway stenosis (the cricoid is much smaller in children than it is in adults).

Emergent intubation is best done by rapid sequence induction, with continuous hemodynamic and pulse oximetry monitoring. In the presence of a cervical spine injury, orotracheal intubation can still be done if the head is secured and inline stabilization is maintained during the procedure, or via a nasotracheal route.

> A patient with multiple stab wounds arrives at the ED. He is conscious. phonating with a normal voice in full sentences, and hemodynamically stable. Upon removal of the dressing he is noted to have an expanding hematoma in the neck.

Although the patient's vital signs and neurological exam are normal, the expanding hematoma is at risk for compromising his airway. This is considered an unprotected airway and requires orotracheal intubation before it becomes an emergency.

Another similar scenario is with a stable patient, but with subcutaneous emphysema in the neck; that would be a marker for impending loss of airway and should be considered unprotected.

> An elderly patient involved in a severe car accident presents with multiple injuries. He is breathing spontaneously, but is not arousable and is not moving his extremities.

Altered mental status is the most common indication for intubation in the trauma patient. Unconscious patients with Glasgow coma score ≤8 may not be able to maintain or protect their airway. Orotracheal intubation is indicated.

> An unconscious man arrives at the ED with spontaneous but noisy and labored breathing. The paramedics explain that at the accident site, the patient was conscious but complaining of neck pain and unable to move his lower extremities. He lost consciousness during the ambulance ride, and efforts to secure a nasotracheal airway were unsuccessful.

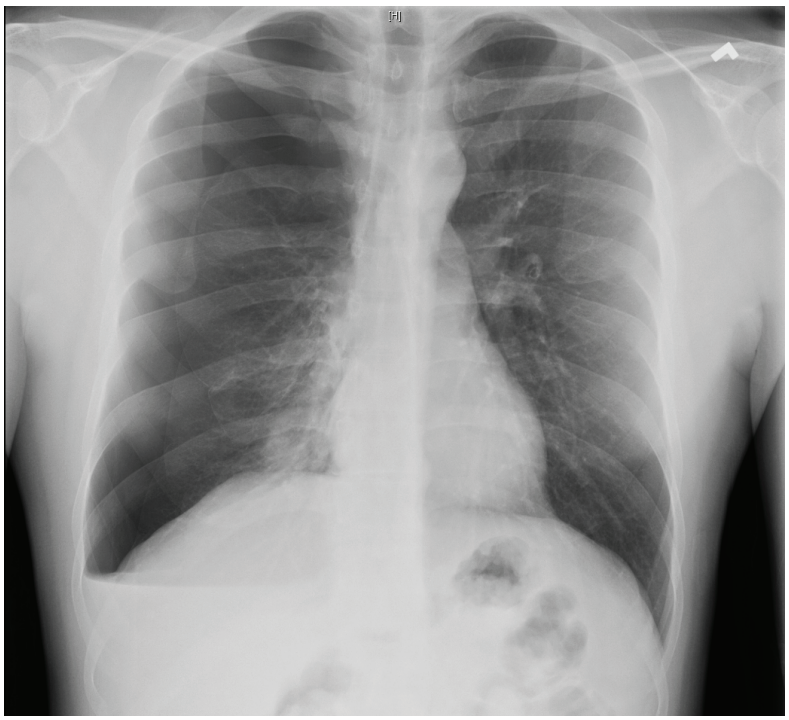
This scenario is intended to convey an unprotected airway with a cervical spinal injury. Orotracheal intubation can still be performed with manual inline cervical immobilization or utilizing a fiberoptic bronchoscope. Nasotracheal intubation is another option if facial injuries do not preclude it.

> A teenager involved in a severe car crash presents with extensive facial fractures and ongoing bleeding from his oropharynx. He is fully awake and alert, but with audible gurgling.

Securing an airway is mandatory here, but orotracheal route may not be possible. Surgical cricothyroidotomy is the best option, with formal tracheostomy later. In a smaller child, tracheostomy should be performed at presentation.

Breathing (B)

The presence of symmetrical breath sounds indicates satisfactory ventilation, while an absence or decrease of breath sounds may indicate a pneumothorax and/or hemothorax (necessitating placement of a chest tube). Pulse oximetry indicates if oxygenation is satisfactory; hypoxia may be secondary to airway compromise, pulmonary contusion, or neurological injury impairing respiratory drive and necessitating intubation. Measurement of end-tidal CO_2 (capnography) is also very useful.



Courtesy of Gary Schwartz, MD

Figure 2-1. Chest X-ray Right Pneumothorax

> An unconscious blunt trauma patient has been rapidly intubated in the ED. He has bilateral breath sounds, and his oxygen saturation by pulse oximetry is 95%.

As far as breathing is concerned, he is moving air and getting oxygen into his blood (oximetry). Deterioration could occur later, but right now we are ready to move to C in the ABCs.

> An unconscious blunt trauma patient has been rapidly intubated in the ED. He has absent breath sounds on the left and his oxygen saturation by pulse oximetry is 86%.

The absence of breath sounds means lack of ventilation of the left lung with subsequent hypoxia. This can be due to inadvertent intubation of the right mainstem bronchus or, alternatively, to a traumatic left pneumothorax. Chest x-ray can confirm the etiology and guide management.

If oxygen saturation were rapidly dropping or hypotension were present, this scenario would be more consistent with a pneumothorax and possibly a tension component. In that case, a left-sided needle decompression followed by chest tube placement would be indicated without a chest x-ray.

Circulation (C)

Shock is the constellation of hypotension, tachycardia, and oliguria representing inadequate organ perfusion. Patients are pale, cold/shivering, sweating, thirsty, and apprehensive. In the most severe cases, impaired perfusion of the brain may lead to unconsciousness. In the trauma setting, this is most often due to **hypovolemia** from hemorrhage (>1,500 mL blood loss), although **cardiogenic** shock can occur due to pericardial tamponade or tension pneumothorax and **neurogenic** shock can occur due to spinal injury.

- **Hemorrhagic shock** is accompanied by collapsed neck veins due to low central venous pressure (CVP), while **cardiogenic shock** causes elevated CVP with jugular venous distention.
- Both processes may occur simultaneously, e.g., a patient could be hemorrhaging and also have a tension pneumothorax.

In pericardial tamponade, there is shock without respiratory distress. With tension pneumothorax, there is significant dyspnea, absent breath sounds and hyperresonance on the side of the tension pneumothorax, and diminished breath sounds on the opposite side (due to mediastinal shift and compression of the lung). Tension pneumothorax can be accompanied by tracheal deviation.

Treatment of hemorrhagic shock includes the following steps (undertaken in the OR or ED depending on the injury and available resources):

- Fluid resuscitation
  - Initial administration is 2 L of lactated Ringer's solution or normal saline unless blood products are immediately available.
  - Resuscitation should be continued until BP and pulse normalize and urine output reaches 0.5–1.0 mL/kg/hr.
  - In the setting of uncontrolled hemorrhage, "permissive hypotension" is recommended to prevent further blood loss while awaiting definitive surgical repair, but a mean arterial pressure >60 mm Hg should be maintained to ensure adequate cerebral perfusion.
  - In the trauma setting, the preferred route is 2 large-bore peripheral IV lines, 16-gauge or greater ("short & fat"); if not possible, insert a central venous catheter. Saphenous vein cutdown is an acceptable alternative. In children <6 years old, intraosseous cannulation of the proximal tibia or femur is the preferred alternative.
- Control of bleeding
  - Transfusion of blood products should be in a 1:1:1 ratio between packed RBCs, fresh frozen plasma, and platelets.

Clinical Pearl

When placing lines for volume resuscitation during hemorrhage, be mindful of the potential location(s) of the traumatic injury. For instance, a femoral venous line with penetrating abdominal trauma may not be very useful in the presence of an IVC or iliac vein injury.

The unstable trauma patient should be rapidly prepared for surgical exploration. This assessment should be underway and appropriate measures taken to head to the operating room during the primary survey—specifically the assessment of circulation.

Pericardial tamponade is a clinical diagnosis that can be confirmed with U/S.

- Management is evacuation of the pericardial space by pericardiocentesis, subxiphoid pericardial window, or thoracotomy. While evacuation is being set up, continue fluid and blood administration to maintain adequate cardiac output.
- In cases of extreme hemodynamic instability or cardiac arrest, emergency left thoracotomy with pericardiotomy is performed in the ED.

Tension pneumothorax is a clinical diagnosis based on physical exam: absent breath sounds, tracheal deviation, "hyperresonance," and distended neck veins. Hypotension and shock will ensue due to decreased venous return to the heart, secondary to elevated intrathoracic pressure. Management requires immediate decompression of the pleural space, initially with a large-bore needle (needle thoracostomy), which converts the tension to a simple pneumothorax. Then place a chest tube.

The fact that a trauma has occurred does not rule out nontraumatic problems causes of shock. Also consider nontraumatic etiologies in the trauma patient. Cardiogenic shock from a myocardial infarction that causes a car accident is a classic example.

Neurogenic/spinal shock is often associated with low BP and bradycardia. It can also result in circulatory collapse. Patients are flushed, "pink and warm," with a low CVP. Treatment is phenylephrine, and fluids aimed at filling dilated veins and restoring peripheral resistance.

> A 22-year-old man arrives at the ED with multiple gunshot wounds to the chest and abdomen. The patient is diaphoretic, pale, cold, shivering, and anxious. He asks for a blanket and a drink of water. Blood pressure is 60/40 mm Hg, while pulse is 150/min and thready.

This is the classic presentation of shock due to penetrating trauma. Although hemorrhage resulting in hypovolemic shock is the most probable etiology, cardiogenic shock due to pericardial tamponade or tension pneumothorax is also possible. Steps in management, done simultaneously, are as follows:

- Large-bore IV lines
- Foley catheter
- Fluid and blood administration
- Preparation for immediate exploratory laparotomy for control of bleeding

Historically, the emphasis in cases of shock was on fluid resuscitation to elevate BP and maintain perfusion. More recently, the focus is on control of the bleeding. This is done manually with rapid assessment of whether there are internal injuries that need surgical exploration for control of hemorrhage, and where these might be.

> A 22-year-old man arrives at the ED with multiple gunshot wounds to the chest and abdomen. The patient is diaphoretic, pale, cold, shivering, anxious, and asking for a blanket and a drink of water. Blood pressure is 60/40 mm Hg and pulse 150/min and thready. Distended veins are visible in his neck and forehead. He has bilateral breath sounds and no tracheal deviation.

This similar scenario now has evidence of pericardial tamponade. A focused abdominal sonography for trauma (FAST exam) could confirm the diagnosis, but time is of the essence. Next steps:

- Evacuate the blood in the pericardial space via pericardiocentesis or surgical exploration (depending on the patient's stability and availability of an OR).
- Left thoracotomy (most rapid technique) can be done in ED if necessary.
- Alternatives include median sternotomy or transdiaphragmatic window at the time of laparotomy.

Clinical Pearl

When assessing the location of a hemorrhage, consider the compartments that might need to be explored–chest, abdomen, retroperitoneum, pelvis, extremities–based on the mechanism of injury. And don't forget "the street," i.e., blood loss that occurred in the field and has now been controlled. The patient may no longer be hemorrhaging, but could still be in shock and require volume resuscitation and/or surgical exploration.

CARPET:

Chest
Abdomen
Retroperitoneum
Pelvis
External
Thigh

- If the chest has been opened, this patient still needs a laparotomy to assess for abdominal damage given the injury pattern.
- Fluid administration and/or blood transfusion would also help with pericardial tamponade, but only until pericardial sac is evaluated.

> A 22-year-old man arrives at the ED with multiple gunshot wounds to the chest and abdomen. The patient has labored breathing and is diaphoretic, cold, shivering, and cyanotic. Blood pressure is 60/40 mm Hg and pulse 150/min and thready. He is in respiratory distress, with no right-sided breath sounds and left-sided tracheal deviation; distended veins are visible in his neck.

This similar scenario describes a tension pneumothorax. Treatment is immediate decompression using a large-bore needle or IV catheter placed into the right pleural space (second intercostal space, midclavicular line), followed by chest tube placement on the right side.

Watch out for chest x-ray as an answer choice—it is a trap. Although it would confirm the diagnosis, pneumothorax is clinically apparent, and time is of the essence. The patient will die while awaiting an x-ray. Exploratory laparotomy will still be needed given the injury pattern.

> A 19-year-old man is shot in the right groin during a drug deal. He staggers to the hospital on his own and arrives at the ED with blood pressure 90/70 mm Hg and pulse 105/min. Bright red blood is squirting from the groin wound.

Control of the bleeding by direct local pressure is the first order of business before volume resuscitation is started. This is done with manual compression or a tourniquet, depending on the scenario. A hemostat (clamp) is not used because it could make the injury worse in that placement is "blind."

> A 4-year-old child has been shot in the arm in a drive-by shooting. The site of bleeding has been controlled by local pressure, but the patient is hypotensive and tachycardic. Two attempts at starting peripheral IVs have been unsuccessful.

Up to age 6, intraosseous cannulation in the proximal tibia or femur is an acceptable route of rapid fluid administration. The initial bolus of Ringer's lactate would be 20 mL/kg of body weight.

A 22-year-old man is involved in a high-speed, head-on motorcycle accident. He arrives at the ED unconscious, with fixed and dilated pupils. He has multiple open fractures in both upper extremities and in the right lower leg. Blood pressure is 70/50 mm Hg, with pulse 140/min.

Shock in the trauma setting is most commonly caused by bleeding, pericardial tamponade, or tension pneumothorax. This case fits right in, but the presence of an obvious head injury might be tricky. On the exam you might be offered various types of intracranial bleeding (epidural or subdural hematoma, subarachnoid hemorrhage) as a source of shock—all would be incorrect. Intracranial bleeding can indeed kill you, but not by blood loss, as there isn't enough room in the head to accommodate the amount of blood needed to go into shock. Appropriate treatment is locating and controlling the source of the bleed prior to evaluating the neurologic injury.

A 72-year-old man who lives alone calls 911 saying that he has severe chest pain. When EMS arrives he is found unresponsive on the living room floor with a laceration to the scalp that is actively bleeding. On arrival at the ED this patient is cold and diaphoretic. Blood pressure is 80/65 mm Hg, and pulse is irregular at 130/min. His neck and forehead veins are distended, and he is tachypneic.

Many findings in this scenario are similar to the previous cases, but the mechanism of trauma seems minimal for such profound hemodynamic instability, and chest pain appears to have preceded the fall. Think of nontraumatic etiologies of similar presentation: cardiogenic shock from a massive MI is most likely.

The next step is EKG. Check coronary enzymes and admit to the coronary care unit. Be careful not to over-resuscitate during the initial trauma evaluation.

A 17-year-old girl is stung several times by a swarm of bees. On arrival at the ED, blood pressure is 75/20 mm Hg and pulse 150/min, but she looks warm and flushed.

Twenty minutes after receiving a penicillin injection, a man breaks into hives and develops wheezing. On arrival at the ED his blood pressure is 75/20 mm Hg and pulse 150/min, but he looks warm and flushed.

In preparation for an inguinal hernia repair, a patient has a spinal anesthetic placed. His level of sensory block is much higher than anticipated. A short while later, blood pressure is 75/20 mm Hg, but he looks warm and flushed.

All of these vignettes describe vasomotor shock due to anaphylaxis or inhibition of the sympathetic nervous system. Treatment is vasoconstrictors and volume replacement.

Disability (D)

Neurologic evaluation (disability) is an important component of the primary survey. Key points include assessing the patient's level of consciousness and ability to move all extremities and open eyes, and as scored by the Glasgow coma scale:

- **Eye**
  1. Does not open eyes
  2. Opens eyes to pain
  3. Opens eyes to voice
  4. Opens eyes spontaneously

- **Verbal**
  1. No sounds
  2. Sounds
  3. Words
  4. Disoriented
  5. Oriented, normal conversation

- **Motor**
  1. No movements
  2. Decerebrate
  3. Decorticate
  4. Flexion/withdrawal to painful stimulus
  5. Localizes pain
  6. Obeys commands

Exposure (E)

Remove the patient's clothing to allow for a thorough physical examination. Check for signs of trauma, bleeding, skin irritations, needle marks, and warm body temperature.

SECONDARY SURVEY

After the primary survey has been completed and any immediate life-threatening emergencies addressed, the trauma evaluation continues with the secondary survey.

- Complete physical exam to evaluate for occult injuries
- Chest x-ray, pelvic x-ray
- Focused abdominal sonography for trauma (FAST exam)
- Foley catheter and gastric tube placement if needed

Note

In real life, the primary and secondary surveys overlap.

Any change in the ABCDEs during the secondary survey requires complete reevaluation.

FAST is a reliable and readily available adjunct to identify intra-abdominal and pericardial fluid. It consists of a bedside U/S that evaluates the perihepatic space, perisplenic space, pelvis, and

pericardium for free fluid. Fluid is not typically present in these locations, so if there is a clinical suspicion such as hypotension following blunt trauma, consider an internal injury.

- An unstable patient with a positive FAST exam needs immediate surgical exploration in the OR.
- A stable patient with a positive FAST exam needs a CT, which is more reliable and may demonstrate the source of the bleeding—typically the liver or spleen.

PHYSICAL EXAM: HEAD TO TOE

Head Trauma

As a rule, **penetrating** head trauma requires surgical intervention and repair of the damage (although a transcranial gunshot wound is often lethal).

- Linear skull fracture with no overlying wounds is left alone.
- Open fracture requires wound closure; if comminuted or depressed, treat in the OR.
- Threshold for obtaining a brain CT should be very low, i.e., do a CT on almost anyone who has lost consciousness or has Glasgow coma score <13.
  - Positive findings need a neurosurgical consult.
  - Normal findings and neurologically intact (Glasgow coma score 15) can be discharged if someone can accompany the patient at home for 24 hours; alternatively, admit for 24 hours of observation and repeat head CT.
  - Normal findings and neurological deficits need further imaging with MRI.
- Basilar skull fracture can be difficult to diagnose. Signs of a fracture affecting the base of the skull include raccoon eyes, rhinorrhea, otorrhea, or ecchymosis behind the ear (Battle sign). CT of the head is required to rule out intracranial bleed and should be extended to include the cervical spine.

Traumatic brain injury (TBI) from trauma has 3 potential etiologies:

- Initial blow/direct cerebral injury; no treatment (other than prevention)
- Intracranial hemorrhage that results in hematoma displacing the brain structures (can relieve with surgery)
- Development of increased intracranial pressure (ICP) due to cerebral edema (can prevent or minimize with medical measures)

Acute epidural hematoma occurs with modest trauma to the side of the head. It has a classic sequence of trauma, unconsciousness, a lucid interval (completely asymptomatic patient), gradual relapse into coma, fixed dilated pupil (90% of the time on the side of the hematoma), and contralateral hemiparesis with decerebrate posturing. CT shows a biconvex, lens-shaped hematoma, typically in the frontotemporal area. Emergency craniotomy produces a dramatic cure.

Acute subdural hematoma also arises from a blow to the head, but the force of the trauma is typically much larger and the patient is usually much sicker, rarely with a period of full consciousness. CT will show a semilunar, crescent-shaped hematoma. If midline structures are deviated, craniotomy to evacuate the blood is indicated, but the prognosis is frequently poor. If there is no deviation, the goal of therapy is to reduce ICP to prevent further damage: invasive ICP monitoring, head elevation, modest hyperventilation, gentle diuresis, and avoidance of fluid overload.

Diffuse axonal injury occurs in more severe trauma, secondary to anoxia or decreased cerebral perfusion. CT shows diffuse blurring of the gray-white matter interface and multiple

Clinical Pearl

Because almost all patients with a history of trauma and unconsciousness (of any length) get a CT scan, the extreme presentation of a fixed pupil and contralateral hemiparesis is seldom seen.

Clinical Pearl

- Cerebral perfusion pressure = mean arterial pressure – intracranial pressure. Accordingly, do not over-diurese to the point of systemic hypotension.
- Hyperventilation is recommended when there are signs of herniation, with goal PCO_2 35 mm Hg.
- Sedation is used to decrease brain activity and oxygen demand. Moderate hypothermia is recommended to further reduce cerebral oxygen demand.

small punctate hemorrhages. Since there is not a discrete hematoma, there is no role for surgery. Therapy is directed at preventing further damage from increased ICP.

Chronic subdural hematoma typically presents in a delayed fashion due to an unrecognized subdural hematoma or expansion of acute subdural hematoma that was not drained. Chronic subdural hematoma may develop from minor trauma, often in older individuals with underlying brain atrophy, from a tearing of the bridging veins. Over several days or weeks, mental function deteriorates as hematoma forms. CT is diagnostic. Treatment is surgical evacuation, which provides dramatic improvement.

> An 18-year-old man arrives at the ED with an ax firmly implanted into his head. Although it is clear from the size of the blade that he has sustained an intracranial wound, he is awake, alert, and hemodynamically stable.

Management of penetrating wound is fairly straightforward, with a few exceptions. As a rule, the damage done to the internal organs (the brain, in this case) will need to be repaired surgically. This man must have the ax removed under anesthesia and with full control in the OR. When a weapon is embedded in the patient with part of it sticking out, do not remove it in the ED or in the field, where uncontrollable bleeding could occur.

> A 48-year-old man is hit over the head with a beer bottle during an assault in a park. He has a scalp laceration, and CT shows an underlying linear skull fracture. He is neurologically intact and gives no history of having lost consciousness.

Clinical Pearl

Hypovolemic shock cannot result from intracranial bleeding, as there simply isn't enough space inside the head for the amount of blood loss needed to produce shock. Look for another source. This is a **classic exam question**.

The rule in skull fracture is that if it is closed (no overlying wound) and asymptomatic, no treatment is required. If it is open (as this one is), the laceration must be cleaned and closed. If it is not comminuted or depressed, the procedure can be done in the ED.

> A 48-year-old man is hit over the head with a beer bottle during an assault in a park. He has a scalp laceration, and CT shows an underlying comminuted, depressed skull fracture. He is neurologically intact and gives no history of having lost consciousness.

The addition to this scenario is a comminuted skull fracture. This requires surgical repair in the OR.

> A 72-year-old pedestrian is struck by a car at an unknown speed. She arrives at the ED with minor bruises and lacerations but is otherwise asymptomatic. She is found to be neurologically intact, although she does not remember the accident. The paramedic reports that she was unconscious at the scene but awoke during the ambulance ride.

Anyone with blunt head trauma who has become unconscious needs a neurologic exam plus CT to assess for intracranial hemorrhage. If both are normal, discharge under supervision is reasonable. If not, admit inpatient and repeat the CT. This scenario is particularly worrisome for an intracranial bleed, given the period of unconsciousness followed by amnesia.

A 72-year-old pedestrian is struck by a car at an unknown speed. She arrives at the ED unconscious. She has ecchymosis around both eyes.

"Raccoon eyes" following blunt head trauma is suspicious for a basilar skull fracture. A CT must be performed, but surgical fixation is rarely necessary. Other potential scenarios include ecchymosis behind the ear, rhinorrhea, and otorrhea, which suggest a CSF leak. These scenarios are typically self-limited but do increase the risk of meningitis. For this reason, systemic antibiotics are indicated.

A 14-year-old boy is hit on the side of the head with a baseball bat. He loses consciousness for a few minutes but recovers promptly and continues to play. An hour later he is found unconscious in the locker room; his right pupil is noted to be fixed and dilated.

This vignette describes an acute epidural hematoma, most likely on the right side. Diagnosis is made with CT scan, which will show a lens-shaped hematoma and deviation of the midline structures to the opposite side. Management is emergency surgical decompression via craniotomy. This condition has a good prognosis if treated but is fatal within hours if it is not.

A 32-year-old man is involved in a head-on, high-speed car crash. He is unconscious at the site, regains consciousness briefly during the ambulance ride, and arrives at the ED in deep coma with a fixed, dilated right pupil and contralateral hemiparesis.

This could also be an acute epidural hematoma, but the high impact mechanism more frequently produces an acute subdural hematoma. Diagnosis is again made with CT scan, which will show a semilunar, crescent-shaped hematoma. Given the lateralizing signs, it will likely demonstrate contralateral midline deviation. Be sure to check the cervical spine! Management requires an emergency craniotomy with evacuation of the clot; this step often leads to significant improvement, particularly when the brain is being pushed to the side, but ultimate prognosis is typically poor due to the accompanying parenchymal injury.

A 32-year-old man is involved in a head-on, high-speed car crash. He is unconscious at the site and arrives at the ED with bilateral fixed dilated pupils. CT of the head shows diffuse blurring of the gray-white mass interface and multiple small punctate hemorrhages. There is no hematoma or displacement of the midline structures.

The CT findings here are classic for diffuse axonal injury. The prognosis is terrible, and there is no role for surgical intervention. Treatment will be directed at preventing further injury from increased ICP, including ICP monitoring, head elevation, hyperventilation, avoidance of fluid overload, gentle administration of mannitol and/or furosemide, and IV sedation and hypothermia to decrease cerebral oxygen demand.

> A 32-year-old man is involved in a head-on, high-speed car crash. He is unconscious at the site and arrives at the ED with bilateral fixed dilated pupils. He has multiple other injuries, including fractures of the lower extremities. Blood pressure is 70/50 mm Hg and pulse 130/min.

Same presentation but with hemodynamic instability. Ignore the neurological deficit for now and focus on identifying a source of bleeding, either external (extremity, scalp, street) or internal (chest, abdomen, pelvis).

> A 77-year-old man is noted by his neighbors to have become progressively forgetful over 3–4 weeks. He used to be active and managed all of his financial affairs. Now he stares at the wall, barely talks, and sleeps most of the day. His daughter recalls that he tripped on his apartment steps and fell about a week prior to the development of symptoms.

This vignette is suspicious for a chronic subdural hematoma. Diagnosis is made with CT; management is surgical decompression via craniotomy. Complete recovery is expected if the condition is recognized and treated appropriately.

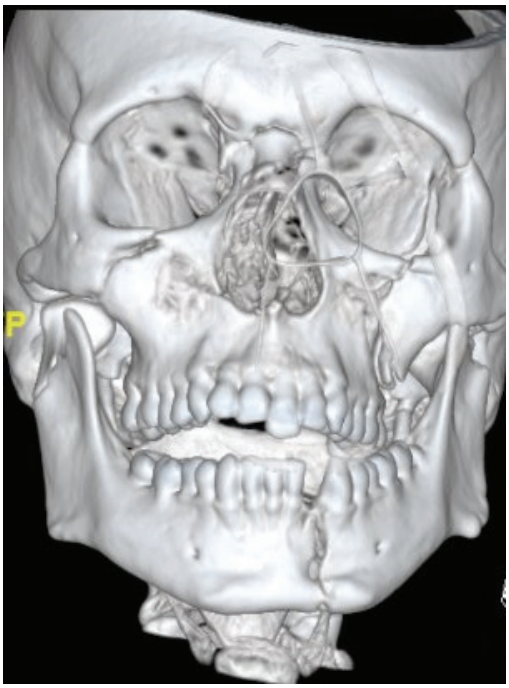
Generally speaking, the indications for surgical intervention in blunt head trauma are **neurologic signs** or **shift of the midline**.

Facial Trauma

The primary concern related to facial fractures in trauma is securing an airway. In the setting of severe facial trauma, orotracheal intubation may be difficult or impossible. In reality, injuries limited to the oropharynx may be managed with nasotracheal intubation, but the safest answer on the exam is a surgical airway: cricothyroidotomy in adults, tracheostomy in children <6 years old.

Severe facial fractures are classified according to the Le Fort system:

- **Le Fort I fracture** is a horizontal fracture pattern resulting in a "floating palate," usually secondary to blunt trauma to the lower maxilla in a downward direction.
- **Le Fort II fracture** is a pyramidal fracture pattern also secondary to blunt trauma to the maxilla, but either directly anterior-posterior or in an upward direction, resulting in fracture of the inferior orbit as well.
- **Le Fort III fracture** includes the above injuries as well as the zygomatic arch, resulting in "craniofacial dissociation."



Courtesy of Gary Schwartz, MD

Figure 2-2. CT Le Fort Fracture

Neck Trauma

To evaluate penetrating neck trauma, the neck is divided into 3 zones from caudad to cephalad:

- **Zone 1** begins at the clavicles and extends up to the level of the cricoid cartilage.
- **Zone 2** is located between the cricoid cartilage and the angle of the mandible.
- **Zone 3** runs from the angle of the mandible to the base of the skull.

Surgical exploration is indicated for an expanding hematoma, deteriorating vital signs, and signs of esophageal or tracheal injury such as coughing or spitting up blood, voice change, or subcutaneous emphysema.

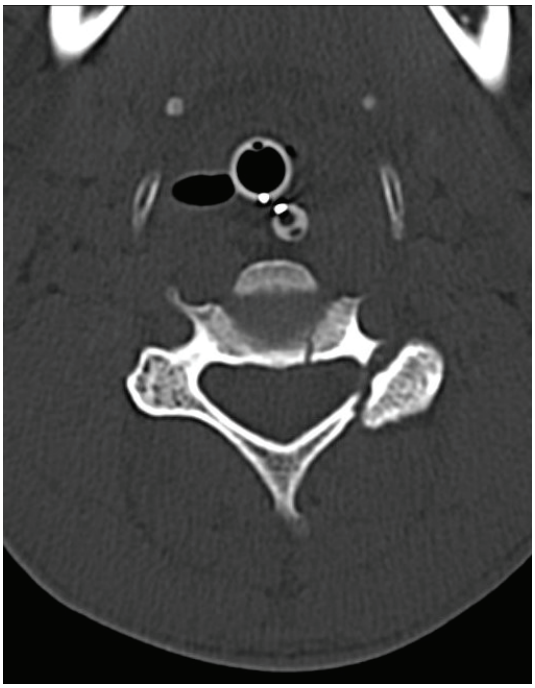
- For injuries to zone 1, evaluate with CT angiogram. If there is radiographic evidence of vascular, airway, or GI tract injury, proceed to the operating room for surgical exploration, bronchoscopy, and esophagoscopy. If CT is negative, further nonsurgical evaluation with esophagram should be considered based on trajectory and CT findings. Bronchoscopy and esophagoscopy may still be necessary, even if a major injury has not been identified on CT.
- Historically, all penetrating injuries to zone 2 mandated surgical exploration. The more recent trend is toward selective exploration based on physical exam and the same imaging studies: CT angiogram to start, esophagram if necessary, and endoscopy as indicated.
- For injuries to zone 3, evaluate with CT angiogram to assess for vascular injury and potential need for angiography and embolization; surgical access to this zone is quite invasive and therefore avoided if possible.

Clinical Pearl

If the patient's condition changes or deteriorates, proceed with urgent surgical exploration—regardless of CT findings.

In all patients with severe blunt trauma to the neck, the integrity of the cervical spine must be ascertained.

- Unconscious patients and conscious patients with midline tenderness to palpation: initially evaluate with CT; depending on findings, possibly follow with MRI
- Conscious patients with no symptoms (i.e., are not intoxicated, have not used drugs, have no "distracting" injury): examine clinically and clear for a cervical spinal injury; if CT of the head is being done, extend the study to include the cervical spine



Courtesy of Gary Schwartz, MD

Figure 2-3. CT C-Spine Fracture

A man has been shot in the neck, and his blood pressure is rapidly deteriorating.

There is not much detail here, but the idea is that penetrating wounds anywhere in the neck need immediate surgical exploration if the patient is unstable. Do not get distracted by the zone of injury. If the patient is unstable, proceed directly to surgical exploration.

A 42-year-old man arrives at the ED after being shot in the neck. A wound is identified in the anterior left side of the neck at the level of the thyroid cartilage. The patient is spitting and coughing blood and has an expanding hematoma under the entrance wound. Blood pressure responded promptly to fluid administration, and he has remained stable.

This is a clear-cut case of a penetrating wound in zone 2 of the neck. The presence of a hematoma and hemoptysis are both highly concerning and are indications for immediate surgical exploration.

A 22-year-old man arrives at the ED after being shot in the neck. A wound is identified above the angle of the mandible with a steady trickle of blood. The patient is drunk and combative but is otherwise stable.

In zone 3 penetrating injuries, there is less concern for a tracheal or esophageal injury—most traumatic injuries are vascular. Given the stability of the patient and difficulty surgically accessing this zone (as it is most difficult to take apart the skull), CT angiogram is still the test of choice. If contrast extravasation is identified, pursue angiography with embolization.

A 22-year-old man arrives at the ED after being shot in the neck. A wound is identified just above the clavicle. The patient is drunk and combative but is otherwise stable.

Unlike zone 3 injuries, zone 1 injuries are very accessible; however, the exact injury will define the surgical approach. Accordingly, in a stable patient, first obtain a CT angiogram to evaluate the need for open surgical exploration. Also evaluate endoscopically with bronchoscopy and esophagoscopy.

Clinical Pearl

Zone 1 injuries can also enter the chest. Make sure to perform a chest x-ray prior to CT angiogram of the neck to rule out pneumothorax or hemothorax.

A 45-year-old woman, an unbelted front passenger during a car crash, was thrown through the windshield at approximately 30 mph. She arrives at the ED strapped to a headboard with multiple facial lacerations but is otherwise hemodynamically stable. Physical examination reveals tenderness to palpation of the posterior cervical midline. Neurological exam is normal.

Every patient with a head injury from blunt trauma is at risk for a cervical spine injury. Pain on palpation raises concern for a serious injury, even in the absence of neurological deficits. Proceed to CT of the neck (and head, given the mechanism of injury). Most likely, an MRI will also be necessary if CT is abnormal or pain persists.

Spinal Cord Injury

The level and mechanism of injury to the spinal cord determines the potential for recovery and therefore the impact on quality of life. Transection of the spinal cord results in irreversible complete loss of motor and sensory neurologic function below the level of the injury. With high spinal cord injury, loss of sympathetic innervation and the resulting vasodilation (and in many cases, loss of sympathetic cardiac drive) can result in neurogenic/spinal shock.

Spinal shock should be considered in the acute trauma setting if there is hypotension and paralysis, which is often accompanied by bradycardia. IV fluids and vasoconstrictors are indicated.

Complete transection results in no function—sensory or motor—below the level of the injury.

Hemisection (Brown-Séquard syndrome), typically caused by a clean-cut injury such as a knife blade, results in ipsilateral paralysis and loss of proprioception along with contralateral loss of pain perception below the level of the injury.

Anterior cord syndrome is typically seen with "burst" fractures of the vertebral bodies. There is loss of motor function, pain sensation, and temperature sensation bilaterally below the injury; vibratory and positional sense are preserved, as the posterior columns are intact.

Central cord syndrome ("whiplash") occurs in the elderly with forced hyperextension of the neck, such as from a rear-end car crash. There is paralysis and burning pain in the upper extremities, but most functions in the lower extremities are preserved.

Management necessitates precise diagnosis of a cord injury, best done with MRI. There is some evidence that high-dose corticosteroids immediately after the injury may help, but that concept is *still controversial.* Further surgical management is too specialized for the exam.

> An 18-year-old man is stabbed in the back, just to the right of the midline, during a bar fight. He has paralysis and loss of proprioception distal to the injury on the right side, and loss of pain perception distal to the injury on the left side.

> A 72-year-old woman is involved in a car crash and sustains T9 and T10 vertebral body fractures. She develops loss of motor function and loss of pain and temperature sensation on both sides distal to the injury, but can feel vibrations and sense position in those areas.

> A 72-year-old woman is rear-ended in a car crash. She subsequently develops paralysis and burning pain on both upper extremities but maintains good motor function in both legs.

These scenarios describe Brown-Séquard syndrome, anterior cord syndrome, and central cord syndrome, respectively. Management depends on an accurate diagnosis. Start with CT to evaluate the bony structures; follow with MRI to evaluate the cord and tendinous structures. Consult neurosurgery for further management.

Chest Trauma

Rib fracture can be deadly in the elderly because the pain impairs respiratory effort, leading to hypoventilation, atelectasis, and ultimately pneumonia. To avoid this cycle, treat pain from rib fractures with a local nerve block or epidural catheter in addition to oral and IV analgesics. Multiple rib fractures have a significant mortality, especially in the older population.

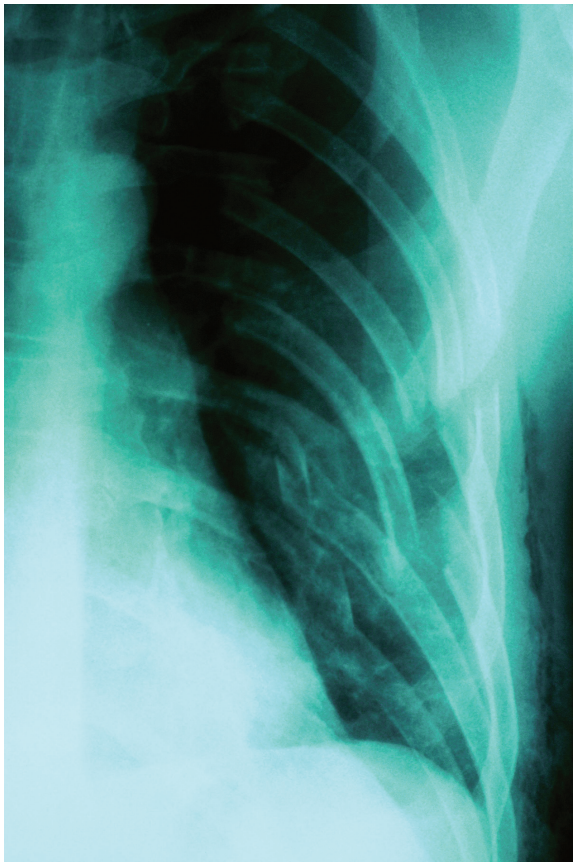


Figure 2-4. X-ray of Multiple Rib Fractures Due to Trauma

Simple pneumothorax is collapse of the lung. It can occur spontaneously but in the setting of trauma can be due to a penetrating injury, rib fracture with puncture of lung, or secondary iatrogenic causes (e.g., central line placement). There is typically moderate shortness of breath with absence of unilateral breath sounds and hyperresonance to percussion. Diagnosis is confirmed with chest x-ray; treatment is chest tube placement.

Hemothorax occurs when a blunt or penetrating injury results in bleeding into the chest cavity. The blood can originate directly from the lung parenchyma or from the chest wall, such as an intercostal artery. Physical examination reveals decreased breath sounds on the affected side accompanied by dullness to percussion.

- Diagnosis is confirmed with chest x-ray, but CT typically aids in diagnosis and surgical planning.
- Treatment is chest tube placement to allow evacuation of the accumulated blood and prevent late development of a restrictive fibrothorax or empyema.
- Surgery to stop the bleeding is sometimes required.
  - If the lung is the source of bleeding, it usually stops spontaneously because it is a low-pressure system.
  - If a systemic vessel, e.g., an intercostal artery, is the source of bleeding, surgical exploration may be necessary to control the hemorrhage. Indications for exploration include:
    - Evacuation of >1,500 mL upon insertion of a chest tube
    - Drainage of >1 L of blood over 4 hours, i.e., >250 mL/hr
    - Hemodynamic instability

Severe blunt trauma to the chest may cause obvious injuries such as rib fractures with a flail chest or sucking chest wound, as well as less apparent injuries such as pulmonary contusion, blunt cardiac injury, diaphragmatic injury, and aortic injury.

Flail chest involves fracture of ≥3 ribs with >2 segments broken per rib. This allows a segment of the chest wall to retract during inspiration and bulge out during expiration ("paradoxical breathing"). The real problem is the underlying pulmonary contusion. A contused lung is very sensitive to fluid overload; thus, treatment includes fluid restriction and aggressive pain management. Pulmonary dysfunction may develop, so serial chest x-rays and arterial blood gases must be monitored. Intubation and mechanical ventilation may become necessary.

Pulmonary contusion may be detected immediately after chest trauma or can be delayed up to 48 hours. It presents with shortness of breath with parenchymal consolidation, which appears as a "white-out" of the affected lung(s) on x-ray. It takes significant force to result in a pulmonary contusion, so also evaluate the patient for traumatic dissection or transection of the aorta using a CT angiogram. ARDS may develop in this scenario.

Blunt cardiac injury should be suspected with the presence of sternal fractures; **it takes great force to fracture the sternum.** EKG monitoring will detect any abnormalities. Historically a serum troponin level was obtained; however, elevations do not generally change management, so this test is not indicated. Treatment is focused on complications of the injury, such as arrhythmias. Obtain an echocardiogram to assess for any structural damage or evidence of a pericardial effusion.

Traumatic rupture of the diaphragm presents with the bowel in the chest on physical exam and x-ray; it is almost always on the left side, as the liver protects the right hemidiaphragm. If diaphragmatic injury is suspected, do laparoscopy to evaluate (although gas insufflation of the peritoneum may complicate anesthetic care). Surgical repair is typically done from the abdomen.

Traumatic rupture of the aorta is the ultimate "hidden injury." It most commonly is due to a significant deceleration injury, and it is located at the junction of the aortic arch and the descending aorta, where the relatively mobile aorta is tethered by the ligamentum arteriosum. This injury may be totally asymptomatic until the hematoma contained by the adventitia ruptures, resulting in rapid death. Suspect aortic injury under the following circumstances:

- There is a high-energy deceleration mechanism
- Widened mediastinum on chest x-ray or mediastinal hematoma on chest CT
- Presence of atypical fractures such as the first or second rib, scapula, or sternum—all require great force to fracture

Diagnosis is made with CT angiogram. As these injuries tend to be delayed, management is deferred until the patient has been stabilized and more immediate life-threatening injuries have been addressed. Repair of aortic injury can then be performed in an open or endovascular route.

Traumatic rupture of the trachea or major bronchus is suggested by the presence of subcutaneous emphysema in the upper chest and lower neck, or by a large "air leak" from a chest tube. Chest x-ray and CT confirm the presence of air outside the bronchopulmonary tree, and fiberoptic bronchoscopy may identify the injury and allow intubation past the injury to secure an airway. Surgical repair is mandatory.

Clinical Pearl

The differential diagnosis of subcutaneous emphysema also includes rupture of the esophagus. Although the pressure of air escaping from the GI tract is typically not enough to cause subcutaneous air tracking, it is possible and so must be ruled out with an esophagram.

Air embolism can produce sudden cardiovascular collapse and cardiac arrest. It should be suspected when sudden death occurs in a chest trauma patient who is intubated and on a respirator. It also can occur in a spontaneously breathing patient if the subclavian vein is opened to the air (e.g., supraclavicular lymph node biopsies, central venous line placement, or lines that become disconnected). Immediate management includes cardiac massage, with the patient positioned in Trendelenburg position with the left side down to "trap" air in the right atrium until it can be absorbed or aspirated.

Fat embolism may also produce respiratory distress in a trauma patient who is without direct chest trauma. The typical setting is the trauma patient with multiple long bone fractures who develops petechial rashes in the axillae and neck; fever, tachycardia, and low platelet count may also be present. Respiratory distress is followed by hypoxemia, with patchy bilateral infiltrates visible on chest x-ray. Management is respiratory support. Adjunctive therapies have been discredited (including heparin, steroids, alcohol, or low-molecular-weight dextran).

> A 75-year-old man slips and falls at home, hitting his right chest wall against the kitchen counter. He has an area of exquisite pain to direct palpation over the seventh rib at the level of the anterior axillary line. Chest x-ray confirms the presence of a rib fracture with hemothorax or pneumothorax.

Rib fracture is the most common chest injury. It is bothersome but manageable in most people. In the elderly, however, it can be hazardous because splinting and hypoventilation lead to atelectasis, which can lead to pneumonia. Treatment is local pain relief with nerve block or epidural catheter and respiratory optimization (supplemental oxygen, incentive spirometry, chest physiotherapy). On the exam, beware of wrong answer choices that might include strapping, binding, or rib plating (rarely indicated as a primary therapy).

> A 25-year-old man is stabbed in the right chest. He is moderately short of breath and has stable vital signs. There are no breath sounds on the right side, which is hyperresonant to percussion.

This vignette describes an uncomplicated pneumothorax. Diagnosis is made with chest x-ray. In this case, unlike a tension pneumothorax, there is time to get an x-ray if the option is offered. Ultimately, management is with insertion of a chest tube. If given an option for location, it should be placed at the fifth intercostal space in the midaxillary line, above the rib.

> A 25-year-old man is stabbed in the right chest. He is moderately short of breath and has stable vital signs. The base of the right chest has no breath sounds and is dull to percussion. Faint breath sounds are auscultated at the apex.

This presentation is consistent with a hemothorax. Diagnosis is made with chest x-ray; if confirmed, treatment is still with a chest tube. This allows drainage to enable ventilation, assess quantity of bleeding, and prevent future empyema or fibrothorax.

A 25-year-old man is stabbed in the right chest. He is moderately short of breath and has stable vital signs. There are no breath sounds at the right base and only faint distant breath sounds at the apex. The right base is dull to percussion. Chest x-ray confirms the presence of a hemothorax. A chest tube placed in the right pleural space drains 400 mL of blood. Over the subsequent 4 hours he continues to drain 200–300 mL of blood/hr, but remains hemodynamically stable.

Hemodynamic instability and volume of chest tube drainage for hemothorax dictate the need for surgical exploration. This scenario qualifies as significant bleeding, probably from a systemic source (e.g., intercostal vessel) rather than the pulmonary parenchyma, which is more likely to resolve spontaneously.

A 54-year-old woman crashes her car against a telephone pole at high speed. On arrival at the ED she is in moderate respiratory distress. She has multiple bruises on the chest and multiple sites of point tenderness over the ribs. X-ray shows multiple rib fractures on both sides, but no hemothorax or pneumothorax.

Clinical Pearl

In cases of blunt trauma with extensive thoracic injuries, don't forget the silent killer: aortic transection. Rule it out with a CT angiogram of the chest.

This common scenario puts the patient at risk for flail chest, as well as pulmonary contusions. Examine for evidence of a flail segment and manage respiratory failure if and when it progresses.

A 54-year-old woman crashes her car against a telephone pole at high speed. On arrival at the ED she is in moderate respiratory distress. She has multiple bruises on the chest and multiple sites of point tenderness over the ribs. X-ray shows multiple rib fractures on both sides, but no hemothorax or pneumothorax. She is admitted to the hospital for pain control. Overnight, she develops severe shortness of breath and is found to have an oxygen saturation of 84%. Chest x-ray shows bilateral infiltrates.

Pulmonary contusions can present in a delayed fashion. Given this patient's trajectory, she is in trouble. She will likely need intubation and mechanical ventilation, ideally with high PEEP. Fluid restriction and diuresis will be helpful if her hemodynamics can tolerate.

A 54-year-old woman crashes her car against a telephone pole at high speed. On arrival at the ED she is in moderate respiratory distress. She has multiple bruises on the chest and multiple sites of point tenderness over the ribs and sternum. X-ray shows multiple rib fractures on both sides and a sternal fracture, but no hemothorax, pneumothorax, or mediastinal hematoma.

This is a variation on the previous scenario with the addition of a sternal fracture, which can be associated with myocardial contusion. Get a 12-lead EKG, but don't check serum troponin levels, as elevation will not affect management. The patient will need continuous monitoring for the development of arrhythmias and a transthoracic echocardiogram to evaluate for a pericardial effusion and to assess ventricular function. Given the force necessary to fracture the sternum, a CT angiogram of the chest to evaluate for aortic transection is again indicated.

A 53-year-old man is involved in a high-speed car crash. He has moderate respiratory distress. Physical examination shows no breath sounds over the entire left chest. Percussion is unremarkable. Chest x-ray shows multiple air-fluid levels in the left chest.

This is a classic presentation of traumatic diaphragmatic rupture with consequent migration of intra-abdominal contents into the left chest; the right side is protected by the liver, so diaphragmatic rupture almost always occurs on the left. A nasogastric (NG) tube curling up into the left chest might be an added clue. In suspicious cases, laparoscopic evaluation is indicated. Management is surgical repair through either the abdomen or the chest, depending on the presence of other injuries and surgeon preference.

A motorcycle daredevil attempts to jump over the 12 fountains in front of Caesars Palace Hotel in Las Vegas. As he leaves the ramp at very high speed, his motorcycle turns sideways and he hits the retaining wall at the other end. In the ED he is found to be remarkably stable, although he has multiple extremity fractures. Chest x-ray shows fracture of the left first rib and a widened mediastinum without pneumothorax or hemothorax.

This is a real case and a classic presentation of trauma aortic transection: significant force, with multiple rib fractures including the first rib. A widened mediastinum is concerning for a major vascular injury and requires a CT angiogram for further evaluation. Management is surgical—either open or endovascular.

A 34-year-old woman presents to the ED following a car crash. She has multiple injuries to her extremities and a scalp laceration. During the course of the evaluation she is noted to have progressive subcutaneous emphysema of her upper chest and lower neck.

There are 3 etiologies of subcutaneous emphysema: pneumothorax, esophageal injury, and a major airway injury. Diagnosis begins with chest x-ray.

- If a pneumothorax is present, place a chest tube.
- If a large continuous air leak is present, suspect a major airway injury and proceed with flexible bronchoscopy.
- If an airway injury is identified, proceed to the OR for surgical repair.
- If no airway injury is identified, rule out an esophageal injury with an esophagram.

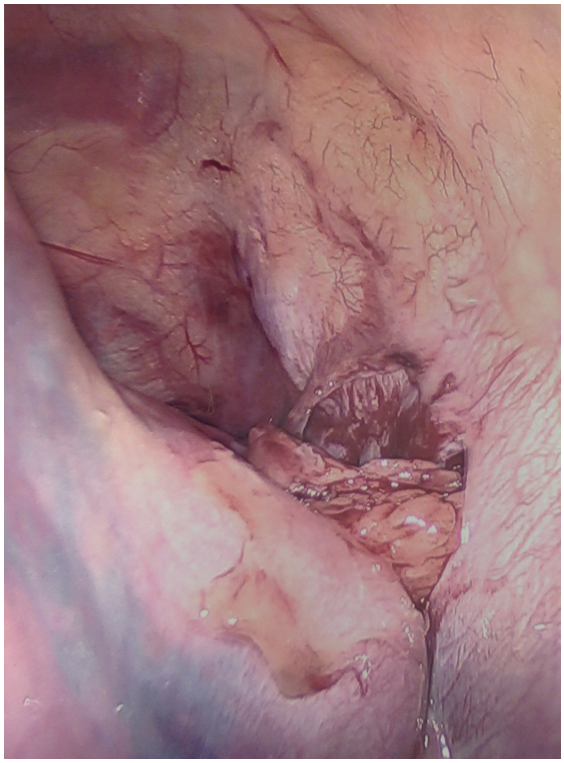
Abdominal Trauma

For the sake of evaluation and management abdominal trauma is divided into penetrating and blunt traumas, based on the mechanism of injury.

Penetrating trauma is further differentiated into gunshot wounds and stab wounds, as the pattern of injury based on these mechanisms is quite different.

Clinical Pearl

The diaphragm separates the thorax and the abdomen, but injuries can occur cross multiple fields. Be aware of potential abdominal injuries with chest wounds and, conversely, chest injuries with abdominal wounds.



Courtesy of Gary Schwartz, MD

Figure 2-5. Transthoracic Transdiaphragmatic Stab Wound

- Gunshot wounds to the abdomen require exploratory laparotomy for evaluation and possible repair of intra-abdominal injuries. Any entrance or exit wound below the nipple line is considered to involve the abdomen.
- Stab wounds allow a more individualized approach. In the presence of protruding viscera or peritoneal signs, proceed to the OR for exploratory laparotomy. In the absence of these signs, some still advocate exploration of the wound in the ED.
  - If the anterior rectus fascia is not violated, no further intervention is necessary.
  - If the anterior rectus fascia is violated, surgical exploration is indicated to evaluate for bowel or vascular injury, even in the setting of hemodynamic stability and lack of peritoneal findings on physical examination. However, this technique is frequently misleading.
- CT scan is most helpful. Safety is the overall primary concern.

Blunt trauma to the abdomen with obvious signs of peritonitis or hemodynamic instability suggesting intra-abdominal hemorrhage requires emergent surgical evaluation via exploratory laparotomy. Signs of internal injury include abdominal distention and significant abdominal pain with guarding or rigidity on palpation.

Even without obvious signs of internal injury, blunt trauma requires further evaluation because intra-abdominal hemorrhage or bowel injury can develop slowly and present in a delayed fashion.

- The unstable trauma patient who has been ruled out for chest and pelvic injuries by physical exam and x-rays needs abdominal exploration.
- The stable blunt trauma patient also needs further evaluation for occult injuries, starting with FAST and progressing to CT scan.

Additionally, CT is helpful in grading the degree of injury and guiding the need for surgical intervention versus observation. In general, intra-abdominal bleeding from the liver or spleen can be observed as long as the patient is hemodynamically stable or responds to fluid and limited blood product administration; the moment instability is mentioned in a vignette, surgical exploration is indicated.

If surgical exploration is performed for penetrating or blunt abdominal trauma, certain principles must be employed.

- Prolonged surgical time and ongoing bleeding can lead to the "triad of death": hypothermia, coagulopathy, and acidosis. The longer a patient is open the worse these components get, and they can interact in a vicious cycle ultimately leading to death. Accordingly, the "damage control" approach has been adopted:
  - Immediate life-threatening injuries are addressed; less urgent injuries are temporized to be addressed later.
  - Immediate life-threatening injuries include hemorrhage and contamination from a GI tract injury. If a bowel resection is necessary, reconstruction can be delayed because only the contamination is life-threatening, not the inability to digest food. Accordingly, resecting the unsalvageable bowel is performed; the GI tract is left in discontinuity requiring future reoperation.
- If hypothermia, coagulopathy, or acidosis is setting in and injuries have been controlled, the operation is terminated and the abdomen is closed in a temporary fashion. The patient is resuscitated in the ICU and returns to the OR at a later date for definitive reconstruction and abdominal closure when warm, not coagulopathic, and not acidotic.
- If coagulopathy does develop during surgical exploration, it is best treated with transfusion of RBCs, fresh frozen plasma, and platelets in equal quantities (**1:1:1 ratio**). This most realistically mimics the replacement of whole blood and provides not only hemoglobin, but also adequate clotting factors to reverse the developing coagulopathy and enable control of hemorrhage.

Clinical Pearl

Whole blood transfusions are now available at major trauma centers.

The abdomen is left open to avoid increasing intra-abdominal pressure due to volume resuscitation and bowel edema, which would otherwise result in **abdominal compartment syndrome**. The elevated pressure leads to decreased perfusion pressure to the viscera, contributing to acute kidney injury and possibly bowel and hepatic ischemia. The diaphragm is displaced cranially, inhibiting efficient ventilation and contributing to respiratory failure. Leaving the abdomen open at the end of a damage-control operation prevents this feared complication and allows for easy access for re-exploration.

Clinical Pearl

Abdominal compartment syndrome can occur in the absence of trauma, when volume resuscitation is significant over a short period of time. This classically occurs in severe pancreatitis. Management is conceptually the same: a decompressive laparotomy to decrease intra-abdominal pressure.

A **ruptured spleen** is the most common source of significant intra-abdominal bleeding in blunt abdominal trauma. Often there are additional diagnostic hints, such as fracture of lower ribs on the left side. Given the limited function of the spleen in the adult, a splenic injury resulting in hemodynamic instability or requiring significant blood product transfusion is an indication for splenectomy. Postoperative immunization against encapsulated bacteria is mandatory (pneumococcus, *Haemophilus influenzae* B, and meningococcus). Lesser injuries to the spleen can be repaired, but for the sake of the examination, perform a splenectomy for unstable patients and manage stable patients nonsurgically.

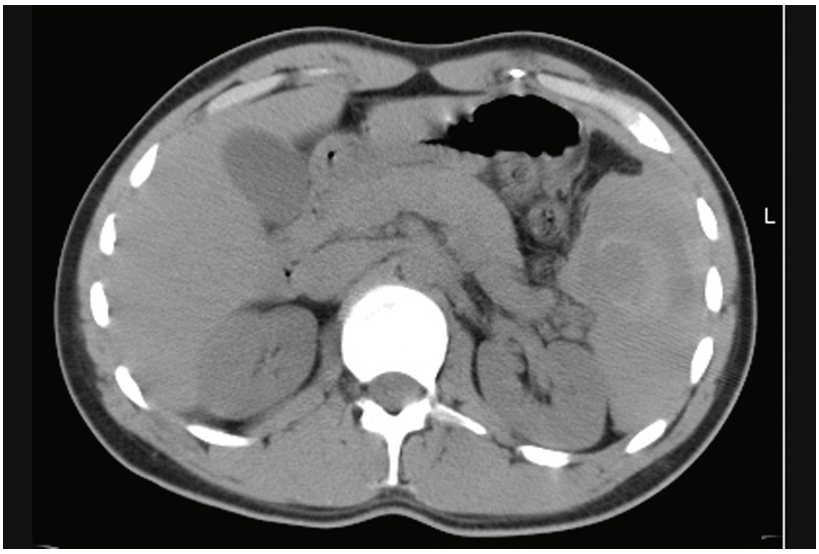


Figure 2-6. CT Ruptured Spleen and Hemoperitoneum

A 19-year-old gang member sustains a gunshot wound to the abdomen. The wound is in the epigastrium to the left of the midline. The patient is hemodynamically stable with minimal abdominal tenderness.

Exploratory laparotomy is needed. Don't be fooled by hemodynamic stability or lack of tenderness; a gunshot wound to the abdomen needs surgical exploration every time. Preparations before surgery include an indwelling bladder catheter, a large-bore venous line for fluid administration, and a dose of broad-spectrum antibiotics.

A 19-year-old gang member sustains a gunshot wound to the abdomen. The wound is in the epigastrium to the left of the midline. The patient is hemodynamically stable with minimal abdominal tenderness. He is taken to the OR for exploratory laparotomy, where a through-and-through injury to the transverse colon is identified.

With minimal contamination, primary repair may be sufficient. If there is a more significant injury or gross contamination is present, bowel resection may be necessary. Historically patients were resected and diverted with an ileostomy or colostomy depending on the location, but there is more recent data to support a primary anastomosis. For the sake of the examination, remain conservative and divert.

A 19-year-old gang member sustains a gunshot wound. On examination a wound is identified just below the right nipple in the midclavicular line. Chest x-ray does not demonstrate a pneumothorax or hemothorax. The patient is hemodynamically stable.

The abdominal cavity extends well into the thoracic cage; consider any penetrating trauma below the level of the nipple to be intra-abdominal. Although no intrathoracic injury is identified on x-ray, this patient needs abdominal exploration.

A 42-year-old man is stabbed in the abdomen in a bar fight. He is hemodynamically stable. On physical exam he elicits no tenderness to palpation. There is a wound to the left of the umbilicus that is not actively bleeding.

A stab wound to the abdomen may not violate the anterior abdominal wall, limiting the possibility of an intra-abdominal injury. Some may explore the wound in the ED, but this can be unreliable. If it does not traverse the anterior rectus fascia, no further workup may be necessary. CT scan is always the safest approach.

A 42-year-old man is stabbed in the abdomen in a bar fight. He is hemodynamically stable. On physical exam he elicits no tenderness to palpation. There is a wound to the left of the umbilicus with protruding omentum.

Stab wounds to the abdomen with clear evidence of fascial penetration require exploratory laparotomy.

A 31-year-old woman is involved in a car accident. Blood pressure is 75/55 mm Hg and pulse 110/min. On physical examination a tender abdomen, with guarding and rebound on all quadrants, is noted.

A 31-year-old woman is involved in a car accident. Blood pressure is 130/80 mm Hg and pulse 80/min. On physical examination a tender abdomen, with guarding and rebound on all quadrants, is noted.

Mechanism of blunt trauma and physical exam suggest an intra-abdominal injury. The point here is that patients can be hemodynamically unstable due to active hemorrhage, but can also be completely stable. The presence of peritoneal signs warrants further evaluation with CT, even in the absence of hemodynamic instability.

A 27-year-old man arrives at the ED having been in a car accident. Blood pressure is 85/68 mm Hg and pulse 128/min. He is tender over the left lower chest wall. Chest x-ray demonstrates fracture of the left 8th, 9th, and 10th ribs without a hemothorax or pneumothorax. CT demonstrates a grade III splenic laceration. He is given 2L of normal saline. Repeat exam reveals blood pressure 78/42 mm Hg and pulse 135/min.

Note

On the exam, you will not be asked about the specific steps of an operation. However, you will need to know the steps for your clinical rotations and your oral examinations, so brush up.

Although this is "only" a grade III laceration, worsening hemodynamics despite volume resuscitation in the presence of a blunt splenic injury is an indication for splenectomy. Proceed to the OR for exploration. Prior to discharge administer Pneumovax and immunize for *Haemophilus influenzae* B and meningococcus.

During an exploratory laparotomy for multiple gunshot wounds to the abdomen, the patient is noted to be 34 C (93.2 F) with oozing from all sites, including IV lines. A ruptured spleen has been removed and a gastric perforation has been repaired.

If the immediate life-threatening bleeding and contamination have been repaired, get out of there. Hypothermia and coagulopathy have already set in; acidosis is not far behind. This "triad of death" is unforgiving. Pack the abdomen, apply a temporary closure, and continue resuscitation in the ICU.

On postoperative day 1 following exploratory laparotomy for blunt trauma with bowel resection and splenectomy, a 27-year-old man complains of worsening abdominal pain. The patient is found to be tachypneic, with abdominal distention and diminishing urine output.

Abdominal compartment syndrome can present in a delayed fashion due to excessive volume resuscitation. Returning the patient to OR for decompressive laparotomy will prevent impending respiratory and renal failure, as well as worsening hemodynamic instability.

Pelvic Fracture

The pelvis is a complete bony ring and therefore cannot be fractured in only one location; multiple fractures are typically present. (Imagine trying to break a pretzel in just one location.) These can range from minor to life-threatening.

Clinical Pearl

With any pelvic fracture, associated injuries must be ruled out:

- Injury to the rectum (evaluate with rectal exam and rigid proctoscopy)
- Injury to the vagina (evaluate with a manual vaginal exam) and urethra (evaluate with a retrograde urethrogram)
- Injury to the bladder

Minor fractures with small pelvic hematomas incidentally identified on CT are typically monitored. In pelvic fractures with ongoing significant bleeding causing hemodynamic instability, management is complex:

- The first step for an obvious pelvic fracture in an unstable patient is external pelvic wrapping to provide some stabilization of the pelvis, thereby limiting the potential space for ongoing blood loss.
- It is difficult to identify and control the source of bleeding in the pelvis, where a deep cavity contains significant organs and vessels including the complex sacral venous plexus. Therefore, angiography is the next step in managing hemorrhage from serious pelvic fracture—not surgical exploration.
- If angiography localizes arterial extravasation, embolization can be hemostatic. If no arterial bleeding is identified, the source is presumed to be venous, and the bilateral internal iliac arteries are prophylactically embolized to proximally control the bleeding.

A 42-year-old woman is thrown from a car during a crash and is crushed underneath the vehicle. Extended extrication is required to get her out. Blood pressure is 92/58 mm Hg and pulse 130/min at the ED, but after administration of 2 L of normal saline, blood pressure 118/68 mm Hg and pulse 110/min. Pelvic x-ray demonstrates a left superior pubic ramus fracture. Focused abdominal sonography for trauma (FAST exam) reveals no intra-abdominal free fluid. CT of the abdomen and pelvis demonstrates no intra-abdominal bleeding, but a hematoma around the fracture.

Nonexpanding pelvic hematomas in a hemodynamically stable patient are initially managed nonsurgically. Blood transfusion may be necessary, and depending on the type of fracture, the orthopedic surgeons may eventually need to stabilize the pelvis. At this time, however, the main issue is to rule out the potential associated pelvic injuries: rectum, bladder, and vagina.

A 42-year-old woman is thrown from a car during a crash and is crushed underneath the vehicle. Extended extrication is required to get her out. Blood pressure is 92/58 mm Hg and pulse 130/min at the ED, but after administration of 2L of normal saline, blood pressure is 88/48 mm Hg and pulse 126/min. Pelvic x-ray demonstrates a left superior pubic ramus fracture. FAST exam reveals no intra-abdominal free fluid. CT of the abdomen and pelvis demonstrates no intra-abdominal bleeding, but a hematoma around the fracture.

This is a similar scenario to the earlier vignette, but the patient is now hemodynamically unstable and not responsive to fluid administration. External pelvic binding to stabilize and transfusion of blood would be the next steps. The big issue will likely be ongoing pelvic hemorrhage. Proceed to interventional radiology for angiography with possible coil embolization.

Urological Injury

The hallmark of traumatic urological injuries is gross hematuria following penetrating or blunt abdominal trauma. Gross hematuria in that setting must be investigated with appropriate studies.

Penetrating urologic injuries as a rule are surgically explored and repaired. Management of **blunt injuries** depends on site:

- Most blunt renal injuries are managed nonsurgically. Hemodynamic instability or contrast extravasation on CT would be an indication for surgical exploration and possible nephrectomy. Renal injuries are secondary to blunt force impacting the flank and are therefore associated with rib fractures.
- Urethral injuries occur almost exclusively in men, as the female urethra is quite short. They are typically associated with a pelvic fracture and typically present with blood at the meatus. Other clinical findings include a scrotal hematoma, the sensation of wanting to void but inability to do so, and a "high-riding" prostate on rectal exam (i.e., it is not palpable on rectal exam). A Foley catheter should not be attempted, as this can compound an existing injury. If it is attempted and meets resistance, attempt should be aborted. A retrograde urethrogram is indicated.
- Bladder injuries can occur in either sex. They are usually associated with pelvic fracture and are diagnosed by retrograde or CT cystogram, including post-void films to enable visualization of extraperitoneal leak that might be obscured by a

Clinical Pearl

Late sequelae for nonsurgical management of blunt renal injury include development of an arteriovenous fistula (leading to high-output heart failure) and renal artery stenosis (leading to hypertension).

bladder full of dye. Management of intraperitoneal bladder injury requires surgical repair with protection by a decompressive suprapubic cystostomy or indwelling Foley catheter.

- Penile fracture (disruption of the corpora cavernosa or the tunica albuginea) occurs to an erect penis, typically during vigorous intercourse. There is sudden pain and development of a penile shaft hematoma, with a normal appearing glans. Frequently, the true history will be concealed by an embarrassed patient. Emergency surgical repair is required. If not done, painful erections and possibly impotence may ensue.

A 22-year-old man is shot in the lower abdomen, just above the pubis. Blood is found in the urine, but on rectal examination there is no evidence of rectal injury.

The hallmark of traumatic urologic injury is hematuria. Penetrating urologic injury is like most penetrating injury elsewhere: it requires surgical repair.

A 22-year-old man is injured in a high-speed car crash and presents to the ED with multiple injuries, including a pelvic fracture. On physical examination there is blood at the meatus.

The vignette on the exam is likely to be longer, but the point is that pelvic fracture plus blood at the meatus in a male means either a bladder injury or (more likely) a urethral injury. Evaluation starts with a retrograde urethrogram. Do not place a Foley catheter, which could compound the injury.

A 22-year-old woman is injured in a high-speed car crash and presents to the ED with multiple injuries, including a pelvic fracture. Insertion of a Foley catheter reveals gross hematuria.

Hematuria in a woman following blunt trauma is most likely to originate in the bladder, given the relatively short urethra. Evaluate with retrograde cystogram. Intraperitoneal extravasation may be seen due to rupture at the dome, but if not visualized, repeat an x-ray after the bladder is empty to potentially visualize retroperitoneal extravasation.

A 22-year-old man is injured in a high-speed car crash and presents to the ED with multiple injuries, including rib fractures and a pneumothorax. Insertion of a Foley catheter results in gross hematuria.

In this case of hematuria following blunt trauma there is no pelvic fracture but there are rib fractures, which are associated with renal injuries. Diagnose with CT scan. Blunt renal injuries can usually be managed nonsurgically; however if hemodynamically unstable, patient may need surgical exploration and possibly nephrectomy.

A 22-year-old man is injured in a high-speed car crash and presents to the ED with multiple injuries, including rib fractures and a pneumothorax. Insertion of a Foley catheter results in gross hematuria, but retrograde cystogram is normal. CT demonstrates a grade II renal injury that is managed nonsurgically. Six weeks later the patient develops acute shortness of breath. Physical examination is significant for normal breath sounds, but a bruit can be auscultated along the flank.

This is a "zebra," but so fascinating that some medical school professors may not be able to resist the temptation to test it. The patient developed a traumatic arteriovenous fistula at the renal pedicle and subsequently developed high-output heart failure. Management is diagnostic arteriogram followed by surgical repair.

In traumatic gross hematuria, both the kidneys and bladder must be evaluated.

Injury to the Extremities

Injury to the extremities can arise from blunt or penetrating mechanisms and can result in orthopedic, soft tissue, vascular, or neurological injuries. Vascular injury has the potential to be immediately life-threatening and should be the initial focus in evaluation. In penetrating injuries of the extremities, the main issue is whether a vascular injury has occurred or not. Anatomic location provides the first clue:

- If there are no major vessels in the vicinity of the injury, only tetanus prophylaxis and irrigation of the wound are required.
- If the penetration is near a major vessel and the patient is asymptomatic, CT angiogram is performed and will guide the need for a surgical intervention.
- If there is an obvious vascular injury (absent distal pulses, expanding hematoma), surgical exploration and repair are required.

Simultaneous vascular and orthopedic injuries pose the challenge of the sequence of operative repair. One perspective is to stabilize the bone first, then do the delicate vascular repair that could otherwise be disrupted by the bony reduction and fixation. However, during the orthopedic repair ongoing ischemia is occurring as the arterial flow is disrupted. A good solution, if proposed on the exam, is to place a vascular shunt, which allows temporary revascularization during the bony repair with subsequent definitive vascular repair. A fasciotomy is usually indicated, as prolonged ischemia could lead to compartment syndrome with irreversible injury.

High-velocity gunshot wounds (e.g. military or big-game hunting rifles) produce a large cone of tissue destruction that requires extensive debridements and potential amputations.

Crushing injuries of the extremities resulting in myonecrosis pose the hazard of hyperkalemia, acidosis, and renal failure, as well as potential development of compartment syndrome. Aggressive fluid administration, osmotic diuretics, and alkalinization of the urine with sodium bicarbonate are good preventive measures for the acute kidney injury. A fasciotomy may be required to prevent or treat compartment syndrome.

Note

A crush injury can result from prolonged lying on a hard floor, where normal movement is prevented by neurologic injury or drugs/alcohol.

A 25-year-old man is shot with a .22-caliber revolver. There is a wound in the anterolateral aspect of his thigh, and the bullet is seen by x-rays to be embedded in the quadriceps posterolateral to the femur.

A 25-year-old man is shot with a .22-caliber revolver. There is a wound in the anteromedial aspect of his upper thigh, and another in the posterolateral aspect of the thigh. There are normal pulses in the leg, and there is no hematoma at the entrance site. X-ray reveals the femur to be intact.

A 25-year-old man is shot with a .22-caliber revolver. There is a wound in the anteromedial aspect of his upper thigh, and another in the posterolateral aspect of the thigh. He has an expanding hematoma in the upper, inner thigh. X-ray reveals the femur to be intact.

Proximity to a major vascular structure is the first thing to assess when assessing penetrating injuries to the extremities. In the first vignette, clearly the trajectory is nowhere near the femoral vessels; therefore no further intervention is warranted (other than tetanus). The second and third vignettes demonstrate that even when you cannot assess what is an entry vs. an exit wound, the proximity to the femoral vessels raises concern for a vascular injury. In the third vignette, there is clear evidence of an arterial injury (expanding hematoma), and this patient should be urgently explored. Although the second vignette does not detail signs of a vascular injury, further investigation with CT angiogram should be performed due to proximity.

A 25-year-old man young man is shot through the arm with a .38-caliber revolver. There are wounds on both the lateral and medial aspect of the extremity, with no radial pulse palpable distally. X-ray demonstrates a shattered humerus.

The lack of a distal pulse is clearly an indication for surgical exploration; the question here is whether to manage the shattered humerus or the vascular injury first. Begin with fracture stabilization, then vascular repair (both artery and vein if possible). The unavoidable delay in restoring circulation will make a fasciotomy mandatory. Temporary shunting the arterial injury to allow distal perfusion is a good solution if offered as a choice, but is easier said than done.

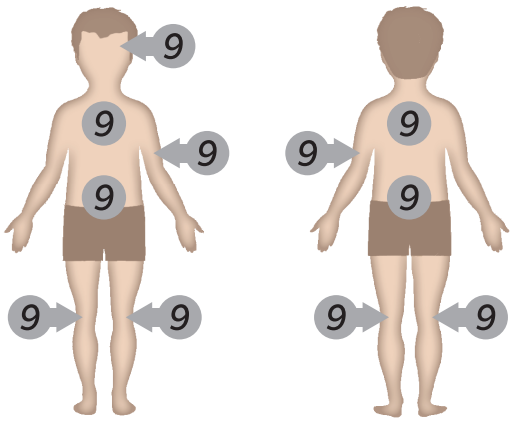
A 6-year-old girl has her hand, forearm, and lower part of the arm crushed in a car accident. The entire upper extremity looks bruised and battered. Pulses are intact, and x-ray demonstrates no fractures.

Crushing injuries lead to 2 concerns in addition to bony or vascular injuries: myoglobulinemia leading to an acute kidney injury, hyperkalemia, and metabolic acidosis; and delayed swelling that may lead to compartment syndrome. For the first, resuscitate with IV fluids, osmotic diuretics (mannitol), and alkalinization of the urine to help protect the kidney. For the latter, perform a fasciotomy.

BURNS

With burns, the loss of skin integrity increases insensible fluid loss, which leads to profound hypovolemia and loss of temperature control. Treatment is as follows:

- In first 24 hours of partial and full thickness burns, fluid resuscitation is guided by the extent of body surface area (BSA) involved; after 24 hours, urine output is main guide for ongoing resuscitation.
- The size of a burn can be estimated by using the tool "**rule of nines**," which divides the BSA into percentages.
  - The head and each upper and lower extremity are each assigned 9% of BSA.
  - Each lower extremity is assigned two 9% units for anterior and posterior.
  - Trunk is assigned 4 units of 9% each: 2 anterior and 2 posterior.
  - Perineum/genitalia is remaining 1% total BSA.
- The Parkland formula is used to estimate the LR replacement fluid needs for burn patients in the first 24 hours (24-hour calculation begins at time of burn injury, not time of presentation).
  - Importance of fluid replacement is to restore circulating volume, enhance tissue perfusion, and preserve vital organs
  - Modified Parkland formula takes body weight (in kilograms) multiplied by the percentage of burn (as a whole number), and multiplied by 4 mL/%TBSA
  - Half of this volume to be infused in first 8 hours
  - Half of this volume to be infused in next 16 hours
- Clean the burn, give tetanus prophylaxis, and use a topical agent (commonly silver sulfadiazine).
  - If deeper penetration is needed, e.g. a thick eschar or a burn over cartilage, mafenide acetate cream is commonly used
  - Burns near the eyes are covered with bacitracin or triple antibiotic ointment (silver sulfadiazine is irritating to eyes)
- After 1–2 days of NG suction, intensive nutritional support is provided, preferably via the gut, with high calorie, high nitrogen diets. Analgesia is initially given IV due to unpredictable GI absorption, but once enteral feeds are started all medications can be given via this route.
- Early excision and skin grafting are recommended to save costs and minimize pain, suffering, and complications.
- Rehabilitation should be started as soon as possible.



Management of burns in infants has several special considerations and therefore warrants transfer to a specialized center.

- Infants have proportionately larger heads and smaller legs than adults (**rule of nines** for infants assigns two 9s to the head and three 9s [not four] for both legs).
- In infants, third-degree burns look deep red, while in adults they have a leathery, dry, gray appearance.
- Infants need proportionally more fluid than adults, so formulas and calculations for them use 4–6 mL/kg/%.

Clinical Pearl

A 70 kg patient with 45% burns would need about 12.6 L of Ringer's lactate solution in the first 24 hours:

- Over first 8 hours: 6.3 L (788 mL/hr)
- Over next 16 hours: 6.3 L (393 mL/hr)

Circumferential full-thickness burns of the extremities can lead to tissue edema and restriction of arterial inflow, resulting in ischemia and compartment syndrome secondary to eschar. This can also occur in circumferential burns to the chest, with resultant limitations in ventilation. Escharotomies of insensate full-thickness burns can be done at the bedside, with no need for anesthesia to provide immediate relief.

Scalding burns in children should always raise the suspicion of child abuse, particularly if the pattern of the burn does not fit the description of the event given by the parents.

Inhalation injuries are caused by flame burns in an enclosed space (e.g., a burning building or car), causing a chemical burn of the tracheobronchial mucosa. Burns around the mouth or soot inside the throat are suggestive clues. Diagnosis is confirmed with fiberoptic bronchoscopy. Treatment is as follows:

- Assess whether respiratory support is necessary and evaluate clinical status
- Get serial arterial blood gases
- Intubate if there is any concern about adequacy of airway
- Monitor carboxyhemoglobin levels

Chemical burns require extensive irrigation to remove the offending agent. Alkaline burns (e.g., from clog remover) are worse than acid burns (e.g., battery acid). Irrigation must begin as soon as possible at the site where the injury occurred (tap water, shower). Do not attempt to neutralize the agent with any chemical reagents.

High-voltage electrical burns are always deeper and worse than they appear. Massive debridement or even amputation may be required. Additional concerns include myonecrosis-induced acute kidney injury, orthopedic injuries secondary to massive muscle contractions (e.g., posterior dislocation of the shoulder, compression fractures of vertebral bodies), and late development of cataracts and demyelination syndromes. Associated arrhythmias can be life-threatening.

> After suitable calculations have been made, a 70 kg adult with extensive third-degree burns is receiving Ringer's lactate at the calculated rate. In the first 3 hours his urinary output is 15, 22, and 18 ml.

The Parkland formula is the classic management of fluid resuscitation in burns and may show up on the exam. However, urine output is the best marker for adequate volume status, and if oliguric (<0.5–1 mL/kg/hr), more fluid is indicated regardless of the Parkland-based calculation.

Adjunctive treatment for burns includes tetanus prophylaxis; topical wound area analgesia; nutritional support; physical therapy; and skin grafting.

> A 42-year-old woman drops her hot iron on her lap while doing the laundry. She comes in with the shape of the iron clearly delineated on her upper thigh. The area is white, dry, leathery, anesthetic.

The description of this burn describes a third-degree burn, but in a limited area. Unlike with extensive burns (even of partial thickness), this patient will not need protracted support. Indeed, with a focal burn, the best management is early excision and grafting.

> A 53-year-old man is brought to the ED after being rescued from a house fire. Burns around the mouth and nose are noted. His pharyngeal mucous membranes are blackened.

There are 2 issues here: carbon monoxide poisoning and respiratory burns due to smoke inhalation from a fire in an enclosed space.

Determine carboxyhemoglobin levels and put the patient on 100% oxygen to shorten its half-life. Serial arterial blood gases will demonstrate the extent of the injury and guide treatment. Bronchoscopy may be helpful for diagnosis, as well as clearance of secretions.

> A 52-year-old man suffers third-degree burns to both arms after his shirt caught fire while lighting a barbecue. The burned areas are dry, white, leathery, anesthetic, and are circumferential around both forearms.

Circumferential burns of the extremities and trunk pose an additional problem: edematous tissue without the ability to expand, leading to increased compartment pressure and ultimately ischemia. Compulsive monitoring of Doppler signals of the peripheral pulses and capillary filling is needed. Emergent escharotomies are indicated if there are signs of ischemia. Chest wall escharotomy is indicated if the burn is limiting ventilation.

> A toddler is brought to the ED with burns on both buttocks. The areas are moist, have blisters, and are exquisitely painful to touch. The parents report that the child accidentally pulled a pot of boiling water over himself.

This vignette describes second-degree burns (in children third-degree burn is deep bright red, rather than white leathery as in the adult.) The same management principles apply, but be on alert for signs of child abuse and appropriate management.

> A frantic mother calls her primary care doctor's office after her 7-year-old girl spilled Drano all over her arms and legs. You can hear the girl screaming in pain in the background.

Chemical injuries, particularly alkali formulas, need immediate copious irrigation. Instruct the mother to do so right at home with tap water, for at least 30 minutes before rushing the girl to the ED. Do not pick an option where you would administer an acidic solution to "neutralize" the chemical burn.

A 42-year-old construction worker accidentally contacts an electrical power line while working on a roof. On physical exam burn wounds are noted on the upper outer thigh and the lower leg on the same side.

Electrical burns are much more significant than they appear. There will be deep tissue myonecrosis, even if it is not apparent on the initial exam. The patient will likely require fasciotomies and surgical debridement. The exam typically focuses on the downstream effects of myonecrosis: myoglobinuria, hyperkalemia, and renal failure. Significant volume resuscitation will be needed, followed by diuresis and alkalinization of the urine.

- Rule out other high-force injuries including posterior dislocation of the shoulder and compression fractures of vertebral bodies (from violent muscle contractions)
- Be aware of the potential for the late development of cataracts and demyelination syndromes

BITES AND STINGS

Tetanus prophylaxis and wound care are required for all bites. Unprovoked bites from dogs or wild animals raise the issue of potential rabies; provoked bites from domesticated dogs are less suspect. If the wild animal can be euthanized, it can be autopsied for signs of rabies; otherwise, rabies prophylaxis with immunoglobulin plus vaccine is mandatory.

Bites

Snakebites do not necessarily result in envenomation, even if the snake is poisonous (up to 30% of bitten patients are not envenomated). The most reliable signs of envenomation are severe local pain, swelling, and discoloration developing within 30 minutes of the bite. If such signs are present, draw blood for typing and crossmatch (cannot be done later if needed), coagulation studies, and liver and renal function.

Treatment is based on antivenin.

- CroFab is preferred agent currently for crotalids (several vials usually needed)
- Antivenin dosage relates to the size of the envenomation, not the size of the patient (children get the same dose as adults).
- Surgical excision of the bite site or fasciotomy is very rarely needed.
- The only valid first aid is to splint the extremity during transportation—**do not make cruciate incisions, suck out venom, wrap with ice, or apply a tourniquet.**

Black widow spiders have a characteristic red hourglass on the belly. Patients with bites experience nausea, vomiting, and severe generalized muscle cramps. Treatment is IV calcium gluconate and muscle relaxants.

Brown recluse spider bites are common, and often not recognized at the time of the bite. These spiders are found in gardens, garages, and basements. In the next several days, a skin ulcer develops with a necrotic center and a surrounding halo of erythema. Surgical debridement of all necrotic tissue is needed, as the venom contains a powerful proteolytic enzyme. Skin grafting may be needed subsequently.

Human bites are the most contaminated and therefore need antibiotic treatment and may require debridement and irrigation in the OR.

Stings

Bee stings kill many more people in the United States than snakebites because of an anaphylactic reaction. Wheezing and rash may occur and rarely may lead to anaphylactic shock. Epinephrine is the drug of choice. The stingers should be removed without squeezing them.

> A 6-year-old child tries to pet a domestic dog while the dog is eating, and the child's hand is bitten by the dog.

This is considered a provoked attack, with a low risk for rabies. Tetanus prophylaxis and standard wound care is all that is necessary.

> While exploring caves in the Texas hill country, a 16-year-old boy is bitten by a bat.

Bats are high risk for rabies transmission; treat with immunoglobulin plus vaccine.

> During a hunting trip, a hunter is bitten in the leg by a snake. The patient arrives at the hospital 1 hour later. Physical examination shows 2 fang marks about 2 cm apart, as well as local edema and ecchymotic discoloration. The area is very painful and tender to palpation.

The local reaction is suspect for envenomation. Blood should be drawn for typing and crossmatch, coagulation studies, and renal and liver function. Treat with antivenin. Surgical excision of the bite site and fasciotomy are only needed in extremely severe cases.

> During a picnic outing, a 6-year-old girl inadvertently bumps into a beehive and is stung repeatedly. Upon arrival to the ED 20 minutes later she is found to be wheezing, hypotensive, and madly scratching an urticarial rash.

This reaction sounds out of proportion to the stings, and likely represents an anaphylactic reaction. Treat with epinephrine.

> A 17-year-old gang member comes to the ED with a 1 cm deep sharp cut over the knuckle of the right middle finger. He says he cut himself with a screwdriver while fixing his car.

The description is classic for a human bite incurred by punching someone in the mouth. Human bites are quite contaminated; start on antibiotics and have a low threshold for surgical exploration.

General Surgery 3

Learning Objectives

- ❏ Understand surgical diseases of the gastrointestinal tract and endocrine systems
- ❏ Recognize surgical etiologies of hypertension
- ❏ List the indications, complications, and alternatives to dermatological procedures

GASTROINTESTINAL

Upper Gastrointestinal Disease

Esophagus

Gastroesophageal reflux disease (GERD) may produce vague symptoms that can be difficult to distinguish from other sources of epigastric distress. Typically, an overweight individual complains of burning retrosternal pain and "heartburn" that is brought on by bending over, wearing tight clothing, and lying flat in bed at night. Patients find relief with antacids and over-the-counter H2 blockers.

- If the diagnosis is uncertain, pH monitoring establishes the presence of reflux and its correlation with symptoms.
- If there is a longstanding history, the concern is that damage might have been done to the lower esophagus (peptic esophagitis) and that Barrett esophagus could develop. In that setting, endoscopy and biopsy are the indicated tests, as Barrett is a precursor to malignancy.

Treatment is as follows:

- H2 blockers or proton pump inhibitors (PPIs) plus lifestyle modification (diet, smoking cessation), which works for most patients
- Surgery may be indicated for symptomatic disease refractory to medical management, intolerance of medication (laparoscopic Nissen fundoplication), and local complications such as ulceration or stenosis (esophagectomy)

Motility problems have recognizable clinical patterns such as crushing pain with swallowing in uncoordinated contraction or dysphagia to solids (but not liquids, as seen in achalasia). Barium swallow is the first step in treatment, to assess for an obstructing lesion, but a definitive diagnosis requires manometry.

Achalasia (women > men) is a functional physiologic obstruction where swallowing becomes difficult and undigested food is occasionally regurgitated. Patients learn that sitting up straight and waiting allows the weight of the column of liquid to overcome the sphincter.

Workup begins with barium esophagram, followed by endoscopy to rule out a mechanical obstruction (e.g., cancer). If not found, manometry is diagnostic. In end-stage achalasia, x-ray demonstrates a severely dilated esophagus ("megaesophagus").

Treatment is endoscopy with dilation and injection of Botox into the lower esophageal sphincter. Because recurrence is high, laparoscopic Heller esophagomyotomy may be required.

Clinical Pearl

Per-oral endoscopic myotomy (POEM) is a new procedure whereby the lower esophageal sphincter is incised endoscopically. Long-term data is still lacking.

Cancer of the esophagus is an obstructive problem that classically presents with progressive dysphagia starting with meat, then other solids, then soft foods, then eventually liquids, and finally (after several months) saliva. Significant weight loss is always seen.

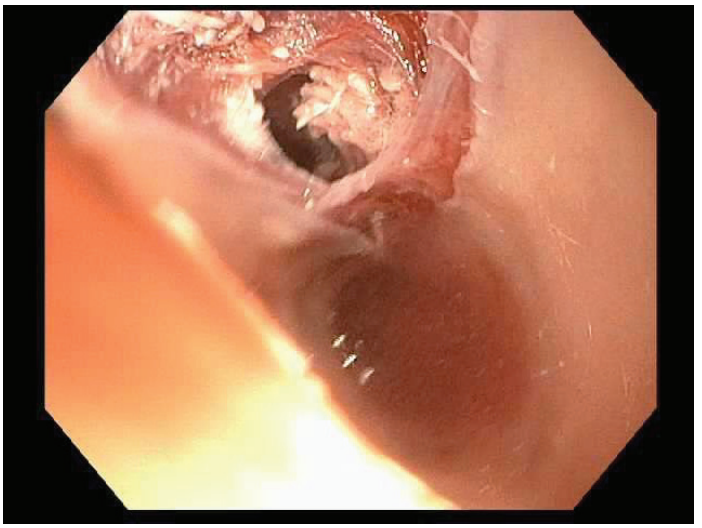
- Squamous cell carcinoma (SCC) is seen in men with a history of smoking and drinking.
- Adenocarcinoma is the more common form of cancer in those with longstanding GERD.

Diagnosis begins with barium esophagram and is confirmed with endoscopy and biopsy. Endoscopic ultrasound (EUS) and CT/PET scan are used to assess local and lymph node involvement, and thus the stage of the cancer. Treatment for early stage lesions is trimodal: chemotherapy, radiation, and surgical resection. Treatment for late stage lesions is chemoradiotherapy (since most are inoperable), but the prognosis is poor.

A **Mallory-Weiss tear** is a mucosal laceration at the junction of the esophagus and stomach. It occurs after prolonged, forceful vomiting and is associated with bright red hematemesis. Endoscopy establishes diagnosis and occasionally allows for treatment with endoscopic clipping or coagulation.

Boerhaave syndrome is rupture (perforation) of the distal esophagus that results from prolonged, forceful vomiting. There is sudden onset of continuous, severe, wrenching epigastric and low sternal pain, followed by fever, leukocytosis, and a very sick-looking patient. A delay in diagnosis and treatment has grave consequences due to the morbidity of mediastinitis.

- Water-soluble contrast esophagram is diagnostic; emergency surgical repair should follow.
- Earlier recognition or limited perforation can be managed endoscopically with esophageal stent placement.
- NPO and nutrition are mandatory; distal enteral feeding (e.g., PEG or jejunostomy) is preferred over TPN.

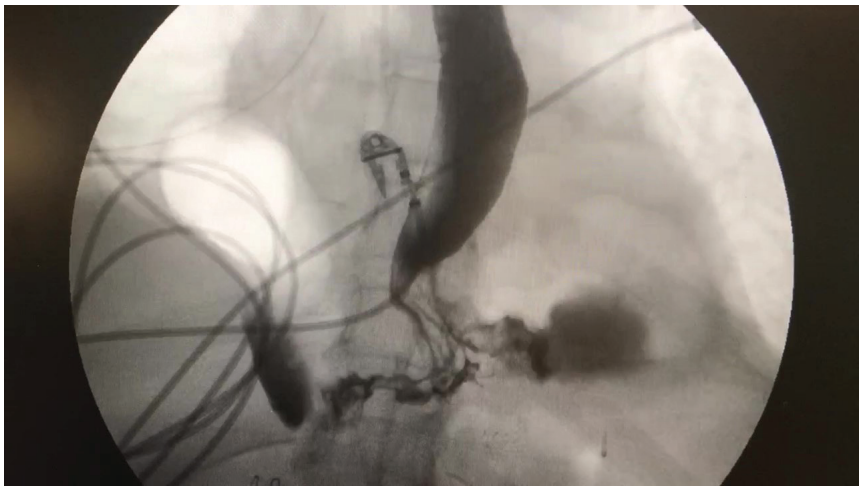


Courtesy of Gary Schwartz, MD

Figure 3-1. Boerhaave's Syndrome

Instrumental perforation is the most common etiology of cervical esophageal perforation. This is most commonly secondary to upper endoscopy but can also occur during cervical spinal instrumentation. Shortly after completion of the procedure, symptoms will develop; immediate post-procedural pain is a perforation until proven otherwise. There may be emphysema in the lower neck (virtually diagnostic in this setting).

- Diagnose with esophagram.
- Treatment is prompt surgical repair (left neck exploration with distal enteral access [e.g. PEG]), which is effective and lifesaving.



Courtesy of Gary Schwartz, MD

Figure 3-2. Upper GI Distal Esophageal Perforation

Stomach

In the past, peptic ulcer disease (PUD) was the most common indication for gastric surgery. In more recent times, the recognition that PUD is caused by *Helicobacter pylori* and the development of highly effective acid-suppressing medications (H2 blockers and PPIs) has dramatically decreased the need for surgical treatment of this condition. Indications for surgery include complications such as perforation.

Gastric adenocarcinoma (elderly > younger) has the following symptoms: anorexia, weight loss, vague epigastric discomfort, early satiety, and occasional hematemesis.

- Diagnose with endoscopy and biopsy; CT helps assess operability.
- Treatment is surgery. Reconstruction depends on the degree of resection, ranging from:
  - No reconstruction (wedge resection)
  - Roux-en-Y gastrojejunal reconstruction (distal resection)
  - Roux-en-Y esophagojejunal reconstruction (proximal or total gastrectomy)

Gastric lymphoma is almost as common as gastric adenocarcinoma. Presentation and diagnosis are similar, but treatment is chemotherapy. Surgery is indicated only if perforation develops as a complication of rapid shrinkage of gastric lymphoma in response to effective chemotherapy.

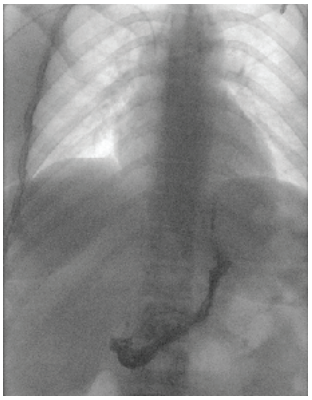
Clinical Pearl

Esophagram utilizing water-soluble contrast (e.g., gastrografin) vs. barium is a classic debate. Barium is much more sensitive, but also more toxic if it aspirates into the tracheobronchial tree or contaminates the mediastinum.

- For the exam, choose *gastrografin*; if the result is negative but you still suspect perforation, repeat with barium.
- In the real world, if the patient is awake and protecting his airway, don't waste time–go with the more sensitive test.

Mucosa-associated lymphoid tissue (MALT) is a low-grade B-cell neoplasm that is associated with *H. pylori* infection. If identified early, MALT neoplasms can be reversed by eradication of *H. pylori*.

Bariatric surgery has gained significant momentum over the past decade for weight loss and reversal of metabolic syndrome. Laparoscopic gastric banding, in which the stomach is externally restricted, resulted in only transient weight loss; with risk of device erosion, it is therefore now rarely performed. Laparoscopic gastric bypass and sleeve gastrectomy are now the preferred techniques, with strict regimens necessary for preserved weight loss and vitamin supplementation. Immediate postoperative risks include staple line and anastomotic leaks, intra-abdominal abscess, and splenic injury.



Courtesy of Gary Schwartz, MD

Figure 3-3. Upper GI Sleeve Gastrectomy

> A 62-year-old man describes epigastric and substernal pain that he cannot characterize well. At times his description sounds like gastroesophageal reflux; at times it does not. Sonogram of the gallbladder, EKG, and cardiac enzymes are negative.

This sounds like GERD, and other etiologies have been ruled out. Perform pH monitoring, which is diagnostic.

> A 54-year-old obese man gives a history of burning retrosternal pain and heartburn that is brought about by bending over, wearing tight clothing, or lying flat in bed at night. He gets symptomatic relief from antacids but has never been formally treated. The problem has been present for many years but seems to be progressing.

The description is classic for GERD. Although symptomatic relief is obtained with antacids, further evaluation should be performed given the chronic nature. This includes *H. pylori* testing and treatment, if indicated, and endoscopy with biopsy to rule out malignant transformation. If any epithelial dysplasia is identified, serial endoscopy is mandatory to evaluate for progression and possible early surgical intervention.

> A 54-year-old obese man gives a history of burning retrosternal pain and heartburn that is brought about by bending over, wearing tight clothing, or lying flat in bed at night. He gets symptomatic relief from antacids but has never been formally treated. The problem has been present for many years and seems to be progressing. Endoscopy shows severe peptic esophagitis and Barrett esophagus.

This patient has not had formal medical treatment, so that should be the first step. Continued symptoms or endoscopic evidence of progression despite medical management would warrant fundoplication; the presence of severe dysplastic changes would be an indication for resection.

> A 54-year-old obese man gives a history of many years of burning retrosternal pain and heartburn that is brought about by bending over, wearing tight clothing, or lying flat in bed at night. He gets brief symptomatic relief from antacids, but despite adherence to a strict program of medical therapy, the process seems to be progressing. Endoscopy shows severe peptic esophagitis with no dysplastic changes.

The patient is not responding to medical management but has no dysplastic changes. This is an indication for surgical fundoplication. Whether or not it is performed, he needs endoscopy surveillance with biopsies to follow progression of the esophagitis.

> A 47-year-old woman describes difficulty swallowing, which she has had for many years. Liquids are more difficult to swallow than solids, and she has learned to sit up straight and wait for the fluids to "make it through." Occasionally she regurgitates undigested food.

This is a classic description of achalasia (a functional physiologic obstruction). Diagnostic testing starts with a barium swallow and is confirmed with manometry. Treatment is endoscopic balloon dilation and Botox injection, but surgical myotomy is often necessary.

> A 54-year-old African American man with a history of smoking and drinking describes progressive dysphagia of 3 months' duration. It began with difficulty swallowing meat, progressed to other solid foods and then soft foods, and is now evident for liquids as well. He locates the place where the food "sticks" at the lower end of the sternum. He has lost 30 pounds of weight.

This scenario is highly worrisome for carcinoma of the esophagus. Given the detail of race, age, sex, and habits, it is probably SCC. Had the history been longstanding reflux, it would suggest adenocarcinoma. Diagnosis and staging include barium esophagram, endoscopy with biopsy and endoscopic U/S, and PET/CT to evaluate for distant disease and determine resectability.

A 24-year-old man spends the night going to bars and drinking heavily. By morning he starts vomiting repeatedly. He initially brings up gastric contents only, but eventually he vomits bright red blood.

A 24-year-old man spends the night going to bars and drinking heavily. By morning he starts vomiting repeatedly. Eventually he has a particularly violent episode of vomiting, and he feels a severe, wrenching epigastric pain and low sternal pain of sudden onset. On arrival at the ED an hour later he still has the pain, is diaphoretic, has fever and leukocytosis, and looks quite ill.

Both of these vignettes have the same beginnings, but one leads to a Mallory-Weiss tear and the other to perforation (Boerhaave syndrome).

- For esophageal bleeding, endoscopy is used to ascertain the diagnosis and occasionally to treat. Bleeding will typically be arterial and brisk, but self-limiting. Photocoagulation can be used if needed, and rarely a discrete mucosal tear is identified that can be clipped.
- For esophageal perforation, the patient is facing a potentially lethal problem. Water-soluble contrast esophagram will confirm the diagnosis, and emergency surgical repair versus endoscopic management will follow. Prognosis depends on the length of time elapsed between perforation and treatment and the degree of mediastinal contamination that has occurred.

A 66-year-old man has an upper gastrointestinal endoscopy done to check on the progress of medical therapy for gastric ulcer. Six hours post-procedure, he returns with complaints of severe, constant retrosternal pain that began shortly after he went home. He looks prostrate and very ill, and is diaphoretic. His temperature is 40 C (104 F) and respiratory rate 30/min. There is a hint of subcutaneous emphysema at the base of the neck.

This is an iatrogenic perforation of the esophagus. The setting plus the air in the tissues are virtually diagnostic. Perform an esophagram, likely to be followed by emergency surgical repair. Severe pain after endoscopy is a perforation until proven otherwise.

Mid and Lower Gastrointestinal Disease

Small bowel

Clinical Pearl

Intestinal obstruction is caused by **A**dhesions, **B**lockage (hernia), or **C**ancer.

Mechanical intestinal obstruction of the small bowel is most often caused by adhesions in those who have had a prior surgery; incarcerated hernias and cancer are the other most common etiologies. Typical symptoms include colicky abdominal pain and protracted vomiting, progressive abdominal distention (if it is a low obstruction), and no passage of gas or feces. Early on, high-pitched bowel sounds coincide with the colicky pain; after a few days, there is silence. X-ray shows distended loops of small bowel with air-fluid levels.

Treatment starts with NPO, NG suction, and IV fluids, watching for either spontaneous resolution or early signs of strangulation or peritonitis. Surgery is done within 24 hours if nonsurgical management is unsuccessful. This typically involves lysis of adhesions but may require bowel resection and anastomosis depending on intraoperative findings.

Strangulation of the intestine occurs when compromised blood supply leads to bowel ischemia. It can result from internal obstruction due to adhesions or external obstruction due to an incarcerated hernia. Either etiology starts as described earlier, but eventually the patient develops fever, leukocytosis, constant pain, signs of peritoneal irritation, and ultimately full-blown peritonitis and sepsis. Emergency surgery is required. A thorough physical exam should demonstrate a hernia if this is etiology. If the hernia is reducible, surgery may be avoided, but the patient still requires observation to rule out ischemia in the now-reduced bowel.

Carcinoid syndrome is seen in patients with a small bowel carcinoid tumor with liver metastases. It includes diarrhea, flushing of the face, wheezing, and right-sided heart valvular damage (look for prominent jugular venous pulse). Diagnose with 24-hour urinary collection for 5-hydroxyindolacetic acid (5-HIAA). Also evaluate the chest for lung and heart lesions—a necessary step.

Treatment depends on the extent of disease, but a typical course is surgical resection and, possibly, adjuvant octreotide.

> A 54-year-old man has had colicky abdominal pain and protracted vomiting for several days. He has developed progressive abdominal distention and has not had a bowel movement or passed any gas for 5 days. High-pitched, loud bowel sounds coincide with the colicky pain. X-ray shows distended loops of small bowel and air-fluid levels. Five years ago he had an exploratory laparotomy for a gunshot wound to the abdomen.

This scenario describes a mechanical intestinal obstruction, most likely caused by adhesions. Manage initially with NG suction, IV fluids, and careful observation.

> A 54-year-old man has had colicky abdominal pain and protracted vomiting for several days. He has developed progressive abdominal distention and has not had a bowel movement or passed any gas for 5 days. High-pitched, loud bowel sounds coincide with the colicky pain. X-ray shows distended loops of small bowel and air-fluid levels. Five years ago he had an exploratory laparotomy for a gunshot wound of the abdomen. A nasogastric tube is placed to low suction and he receives IV fluids. Six hours later he develops fever, leukocytosis, abdominal tenderness, and rebound tenderness.

This scenario has now progressed to strangulation, i.e., a loop of bowel that was incarcerated is now ischemic. Emergency surgical exploration is now necessary.

> A 54-year-old man has had colicky abdominal pain and protracted vomiting for several days. He has developed progressive abdominal distention and has not had a bowel movement or passed any gas for 5 days. High-pitched, loud bowel sounds coincide with the colicky pain. X-ray shows distended loops of small bowel and air-fluid levels. On physical examination a groin mass is noted. The patient explains that he used to be able to "push it back" at will, but for the past 5 days has been unable to do so.

This is mechanical intestinal obstruction caused by an incarcerated hernia. Fluid resuscitation should be initiated and gentle reduction attempted. If the hernia is irreducible or there is evidence of bowel ischemia (i.e., it is strangulated), then urgent surgical exploration is indicated.

Clinical Pearl

Whenever hormone-driven or paraneoplastic syndromes produce episodic attacks, the offending agent will be at high serum concentrations only at the time of the attack—not continuously. Accordingly, a blood sample taken after the episode will often be normal. A 24-hour urine collection is much more sensitive.

A 55-year-old woman is being evaluated for protracted diarrhea. On further questioning she gives a history of episodes of flushing of the face, with expiratory wheezing. A prominent jugular venous pulse is noted on her neck.

This is carcinoid syndrome. Diagnosis is made with 24-hour urinary collection for 5-hydroxyindolacetic acid, CT of the chest and abdomen to assess for lung or liver lesions, and transthoracic echocardiogram to assess for cardiac involvement. Octreotide scan is a nuclear medicine scan that can localize a lesion if not found. Management will likely include surgical resection depending on imaging findings.

Clinical Pearl

Patients with acute appendicitis do not always present with classic findings, especially women of childbearing age where ovarian pathology or a retrocecal appendix may present similarly. CT has become the standard diagnostic modality for those cases, but U/S is preferred for children because of the proven negative effects of radiation in children.

Note

Once a colonic malignancy is discovered, the entire colon must be evaluated to look for synchronous cancers.

Colon

Acute appendicitis is one of the most common GI conditions requiring emergency surgery. The clinical presentation provides important diagnostic clues. The classic picture begins with anorexia followed by periumbilical crampy pain that progresses to sharp, severe pain localizing to the right lower quadrant (RLQ). On physical exam, localized tenderness, guarding, and rebound are found in the RLQ. Fever is typically low-grade. Leukocytosis is present in the 10–20K range, with neutrophilia and bandemia. Urgent appendectomy is curative.

Cancer of the right colon typically presents with anemia (hypochromic, iron deficiency) in the right age group (age 50–70). Stools will be 4+ for occult blood.

- Diagnose with colonoscopy and biopsies
- Treatment is surgical resection via right hemicolectomy

Cancer of the left colon typically presents with bloody bowel movements and obstruction. Blood coats the outside of the stools, which may have narrow caliber, and there may be constipation.

- Diagnose first with flexible proctosigmoidoscopy exam and biopsies
- Before surgery is done, full colonoscopy is needed to rule out a synchronous second primary lesion that is more proximal
- CT helps assess operability and extent
- Treatment
  - Nonobstructing lesions: elective surgical resection (sigmoidectomy or left hemicolectomy) and primary anastomosis
  - Acute obstructing lesions: resection with a diverting colostomy

Colonic polyps may be premalignant. In descending order of probability for malignant degeneration, these are familial polyposis (and variants such as Gardner syndrome), familial multiple inflammatory polyps, villous adenoma, and adenomatous polyp. Polyps that are not premalignant include juvenile, Peutz-Jeghers, isolated inflammatory, and hyperplastic.

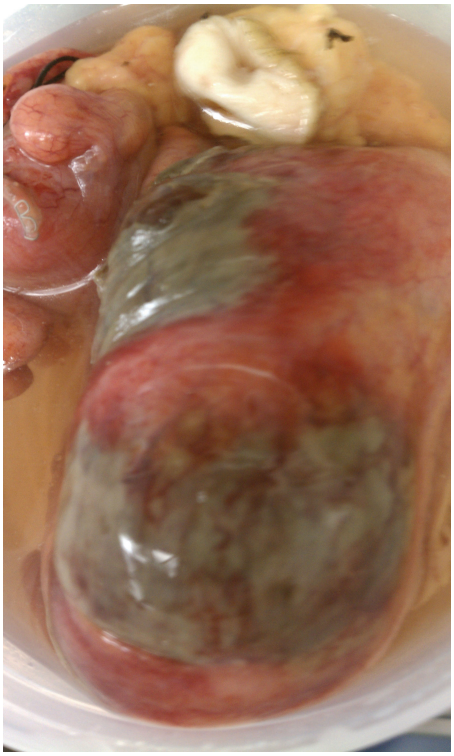
Inflammatory bowel disease (IBD) is divided into **Crohn's disease** and **ulcerative colitis (UC)**. Diagnosis is made with colonoscopy with biopsy. Treatment is primarily medical.

- Crohn's disease can affect the entire length of the GI tract, while UC is limited to the colon.

- UC can be cured with surgical resection (total colectomy with ileoanal anastomosis, often with a temporary diverting ileostomy). Indications for surgery include the following:
  - Disease present >20 years (due to very high incidence of malignant degeneration)
  - Severe interference with nutritional status
  - Multiple hospitalizations
  - Need for high-dose steroids or immunosuppressants
  - Development of toxic megacolon (abdominal pain, fever, leukocytosis, epigastric tenderness, massively distended transverse colon on x-rays with gas within the wall of the colon)

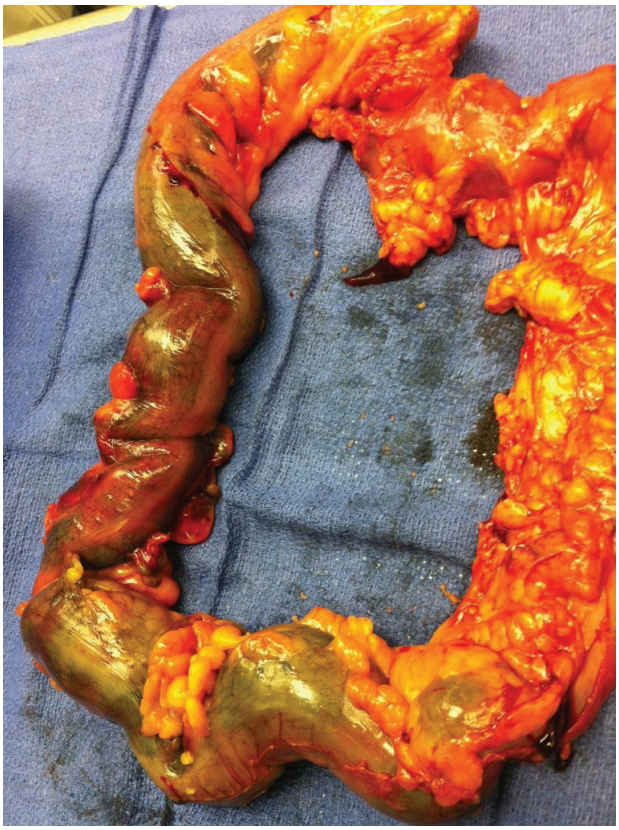
Clostridium difficile overgrowth due to the use of antibiotics and interruption of the normal intestinal flora can result in severe colitis ("pseudomembranous colitis"). Clindamycin was the first antibiotic identified as a culprit; however, any antibiotic and any dose can cause this syndrome of profuse, watery diarrhea, crampy abdominal pain, fever, and leukocytosis.

- Diagnosis is identification of the toxin in the stool. Stool culture takes several days, and the pseudomembranes are not always seen on endoscopy.
- Treatment is immediate discontinuation of the culprit antibiotic (do not use antidiarrheals) and metronidazole (preferred) or vancomycin once the diagnosis is definitively made.
  - A virulent form of the disease, unresponsive to treatment, with WBC >50,000/μL and serum lactate >5 mg/dL, requires emergency colectomy.
  - Fecal transplantation to restore normal gut flora may be needed for those with recurrent infections.



Courtesy of Gary Schwartz, MD

Figure 3-4. Colonoscopy of Pseudomembranous Colitis



Courtesy of Gary Schwartz, MD

Figure 3-5. Toxic Megacolon

A 22-year-old man develops anorexia followed by vague periumbilical pain that several hours later becomes sharp, severe, constant, and well localized to the right lower quadrant of the abdomen. He has abdominal tenderness, guarding, and rebound to the right and below the umbilicus, temperature 37.55 C (99.6 F), and white blood cell count 12,500 with neutrophilia.

This is a classic description of acute appendicitis. Management is emergency appendectomy. CT would not be indicated in this case, but in atypical cases it is diagnostic. In children, U/S is preferred.

A 59-year-old man is referred for evaluation because he has been fainting at his job where he operates heavy machinery. He is pale, but otherwise his physical examination is remarkable only for 4+ occult blood in the stool. Lab shows hemoglobin level 5 g/dL.

This scenario is cancer of the right colon until proven otherwise. Diagnosis is made with colonoscopy and biopsy. Treatment is blood transfusion and eventual right hemicolectomy.

A 56-year-old man has bloody bowel movements. The blood coats the outside of the stools and has been present on and off for several weeks. For the past 2 months he has been constipated, and his stools have become of narrow caliber.

This is cancer of the distal, left side of the colon. Diagnosis is made with endoscopy and biopsy. Treatment is flexible proctosigmoidoscopy first, but a full colonoscopy and surgical resection will likely be needed.

A 42-year-old man with a 20-year history of chronic ulcerative colitis has had at least 40 hospital admissions for exacerbation of the disease. Because of a recent relapse, he has been placed on high-dose steroids and azathioprine. For the past 12 hours he has had severe abdominal pain, temperature 40 C (104 F), and leukocytosis. He looks ill and "toxic." He weighs 90 pounds. His abdomen is tender, particularly in the epigastric area, and there is muscle guarding and rebound. X-ray shows a massively distended transverse colon and gas within the wall of the colon.

This is toxic megacolon. Treatment is emergency total colectomy. Rectal mucosa can harbor residual colitis, so the entire colon must be removed.

- In the elective setting for chronic UC, reconstruction with an ileoanal anastomosis (with or without a temporary diverting ileostomy) can be performed.
- In the setting of toxic megacolon in a sick patient, resection with end ileostomy is the most rapid and lifesaving procedure. If and when the patient recovers, he may be able to have reconstruction with an ileoanal anastomosis.

A 27-year-old man is recovering from an appendectomy for gangrenous acute appendicitis with perforation and periappendiceal abscess. He has been receiving clindamycin and tobramycin for 7 days. Eight hours ago he developed watery diarrhea, crampy abdominal pain, fever, and leukocytosis.

This is worrisome for *Clostridium difficile* colitis. The diagnosis relies primarily on identification of toxin in the stools. Cultures take too long, and a proctosigmoidoscopy exam does not always find typical changes.

Treatment is to stop the clindamycin, stay away from antidiarrheal medications, and treat with metronidazole (oral or IV) or oral vancomycin once the diagnosis is definitively made. Failure of medical management, with development of marked leukocytosis and lactic acidosis, is an indication for emergency colectomy.

Anorectal Disease

Cancer should always be considered in anorectal disease, even if a clinical presentation suggests a benign process. This requires at minimum a thorough physical exam, and a possible colonoscopy depending on the degree of suspicion.

Hemorrhoids typically bleed when they are internal and hurt when they are external; internal hemorrhoids can become painful and produce itching if they prolapse. Internal hemorrhoids can be treated with rubber band ligation, whereas external hemorrhoids

(especially thrombosed external hemorrhoids) may require surgery after failure of conservative measures (e.g., dietary adjustments, increased fiber, sitz baths).

Anal fissures produce exquisite pain, with defecation and blood streaks in stools. The fear of pain is so intense that patients avoid bowel movements and may even refuse proper physical examination of the area. A tight sphincter or a very large, hard bowel movement with straining is believed to both cause and perpetuate the problem.

- Examination may need to be done under anesthesia (the fissure is usually posterior, in the midline).
- Treatment is directed at relaxing the sphincter: stool softeners, topical nitroglycerin, topical CCBs (diltiazem 2% ointment), local injection of botulinum toxin, steroid suppositories, or lateral internal sphincterotomy if there is no improvement.

Crohn's disease can involve the anal area. It starts with a fissure, fistula, or small ulceration. Suspect this diagnosis when the area fails to heal or gets worse after surgical intervention (in general, the anal region heals quickly due to its extensive vascularity). For this reason, surgical intervention for perianal diseases in patients with Crohn's disease should be avoided. A fistula, if present, could be drained with setons while medical therapy is underway. Remicade helps healing.

Ischiorectal abscess (perirectal abscess) is a very common problem. Patients typically present with fever and exquisite perirectal pain that does not let them sit down or move their bowels. Physical exam shows all the classic findings of an abscess (rubor, dolor, calor, and fluctuance) lateral to the anus, between the rectum and the ischial tuberosity. Incision and drainage are needed, and cancer should be ruled out by proper examination during the procedure. If patient is a poorly controlled diabetic, necrotizing soft tissue infection may follow. Significant monitoring is mandatory.

Fistula-in-ano develops in some patients who have had an ischiorectal abscess drained. Epithelial migration from the anal crypts (where the abscess originated) and from the perineal skin (where the drainage was done) form a permanent tract. Patient reports fecal soiling and occasional perineal discomfort. Physical exam shows an opening lateral to the anus or a cordlike tract, and discharge may be expressed. Rule out a necrotic and draining tumor, and treat with fistulotomy.

SCC of the anus is rare, but more common in patients with HIV or who have anoreceptive intercourse. A fungating mass grows out of the anus, and metastasis to inguinal nodes are often palpable. Diagnose with biopsy. Treatment starts with the Nigro protocol of chemoradiation (5-fluorouracil, mitomycin, and external beam radiation), followed by surgery if there is residual tumor. Chemoradiation has a 90% success rate, so surgery is not often required.

> A 60-year-old man known to have hemorrhoids reports bright red blood on toilet paper after evacuation.

> A 60-year-old man known to have hemorrhoids complains of anal itching and discomfort, particularly toward the end of the day. He has mild perianal pain when sitting down and finds himself sitting sideways to avoid the discomfort.

On the exam, reassurance and over-the-counter remedies will be provided as distractors, but in all anorectal problems cancer must be ruled out first.

- Diagnose with proctosigmoidoscopy examination and rule out cancer: digital rectal exam, anoscopy, and consideration of flexible sigmoidoscopy versus complete colonoscopy

- Treatment
  - Internal hemorrhoids: rubber-band ligation
  - External hemorrhoids or prolapsed internal hemorrhoids: surgery

> A 23-year-old woman describes exquisite pain with defecation and blood streaks on the outside of the stools. Because of the pain she avoids having bowel movements. When she finally does, the stools are hard and even more painful. Physical examination cannot be done, as she refuses to allow anyone to even draw apart her buttocks to look at the anus for fear of precipitating the pain.

This is a classic description of anal fissure. Nonetheless, cancer still must be ruled out. Examination under anesthesia is the correct answer. Medical management includes stool softeners and topical agents. A tight sphincter is believed to cause and perpetuate the problem; it can be treated with topical diltiazem, botulin injections, or steroid suppositories. If these fail, lateral internal sphincterotomy is the operation of choice.

> A 28-year-old man is brought to the office accompanied by his mother. In the last 4 months he has had 3 operations—done elsewhere—for a perianal fistula, though after each one the area has failed to heal; in fact, the surgical wounds have become bigger. The patient now has multiple nonhealing ulcers, fissures, and fistulas all around the anus, with purulent discharge. There are no palpable masses.

The perianal area has a fantastic blood supply and heals beautifully even though feces bathe the wounds. When it does not heal rapidly, immediately think of Crohn's disease. You must still rule out malignancy (anal cancer also does not heal if incompletely excised); a proper examination with biopsies is needed. Fistulotomy is not recommended in this setting. Most fistulae will eventually resolve with draining setons, which will ensure adequate drainage of infection while medical management controls the disease. Remicade in particular has shown to help heal these fistulae.

> A 44-year-old man shows up in the ED at 11 p.m. with exquisite perianal pain. He cannot sit down, reports that bowel movements are very painful, and is experiencing chills and fever. Physical examination shows a hot, tender, red, fluctuant mass between the anus and the ischial tuberosity.

This case describes another very common problem: ischiorectal abscess. The treatment for any abscess is drainage, and this one is no exception. However, cancer must also be ruled out, so the best option is examination under anesthesia and incision and drainage. If the patient is diabetic, incision and drainage would have to be followed by minute in-hospital follow-up.

A 62-year-old man complains of perianal discomfort and reports that there are fecal streaks soiling his underwear. Four months ago he had a perirectal abscess drained surgically. Physical examination shows a perianal opening in the skin, and a cordlike tract can be palpated going from the opening toward the inside of the anal canal. Brownish purulent discharge can be expressed from the tract.

This scenario describes fistula-in-ano. Management is to first rule out cancer with proctosigmoidoscopy (necrotic tumors can drain), then schedule an elective fistulotomy.

A 55-year-old HIV-positive man has a fungating mass growing out of the anus, and rock-hard, enlarged lymph nodes in both groins. He has lost a lot of weight and looks emaciated and ill.

This clinical picture is most consistent with SCC of the anus. Diagnosis is made with biopsy of the fungating mass. **Nigro protocol** is combined preoperative chemotherapy and radiation for 5 weeks, and cure rate is 90%. Surgery is done only if this regimen fails to cure the cancer.

Gastrointestinal Bleeding

In 75% of cases, gastrointestinal (GI) bleed originates in the upper GI tract (from tip of the nose to ligament of Treitz), and in 25% of cases it originates in the colon or rectum. Very few cases arise from the jejunum and ileum.

GI bleed in young patients most commonly originates in the upper GI tract (gastritis or PUD), whereas GI bleed in older patients originates from upper or lower sources. Note that GI bleed in lower sources increases with age: angiodysplasia, polyps, diverticulosis, and cancer.

Vomiting blood (hematemesis) always denotes a source in the upper GI tract. The same is true when blood is recovered by an NG tube in a patient who presents with bleeding per rectum. The best next diagnostic test in that setting is upper GI endoscopy. Be sure to look at the mouth and nose first.

Similarly, **melena** (black, tarry stool) always indicates digested blood, thus it must originate high enough to undergo digestion. Start the workup with upper GI endoscopy.

Bright red blood per rectum (hematochezia) could come from anywhere in the GI tract, including upper GI, as it may have transited too fast to be digested.

If the patient is actively bleeding at the time of arrival, the first diagnostic step is to pass an NG tube and aspirate gastric contents to assess if the bleeding is from the upper GI tract and, of course, to prevent aspiration.

- Retrieval of blood establishes an upper source; follow with upper endoscopy as previously described.
- Fluid with no blood and no bile excludes the territory from the tip of the nose to the pylorus, but the duodenum is still a potential source; upper endoscopy is still necessary.
- If no blood is recovered and the fluid is green (bile tinged), the entire upper GI (tip of nose to ligament of Treitz) has been excluded; upper endoscopy is not necessary.

Note

The challenge with the tagged red-cell study is that it is a slow test. By the time it is finished patients have often stopped bleeding, so a subsequent angiogram is useless. However, at least the localization of bleeding helps to identify which side of the colon to resect should the patient rebleed or emergently begin to exsanguinate.

Active bleeding per rectum, when upper GI has been excluded, is more difficult to work up. Bleeding hemorrhoids should always be excluded first by physical exam and anoscopy. Colonoscopy is not helpful during an active bleed, as blood obscures the field. Once hemorrhoids have been excluded, further diagnosis is based on the rate of bleeding.

- If bleeding exceeds 2 mL/min (1 unit of blood every 4 hours), do an angiogram, which is likely to find the source and may allow for angiographic embolization.
- If bleeding is slower, i.e., <0.5 mL/min, wait until it stops; then do a colonoscopy.
- For bleeding in between these rates, do a tagged red-cell study:
  - If the tagged blood collects somewhere, indicating a site of bleeding, do an angiogram.
  - If the tagged red cells do not show up on the scan, plan a colonoscopy. Some practitioners always begin with the tagged red-cell study regardless of the estimated rate of bleeding.

When bleeding is not found to be in the colon, capsule endoscopy is done increasingly often in clinical practice to localize the spot in the small bowel. Obviously, this is done only when the patient is stable and upper/lower GI sources have been ruled out.

Patients with a recent history of blood per rectum but no active bleed at the time of presentation should start workup with upper GI endoscopy if they are young (overwhelming odds). Patients who are old need both an upper and a lower GI endoscopy (typically performed during the same session).

Blood per rectum in a child is most commonly a **Meckel's diverticulum**. Diagnose with a technetium scan, looking for the ectopic gastric mucosa in the distal ileum.

Massive upper GI bleeding in the stressed, multiple-trauma, or complicated post-op patient is probably from stress ulcers in the stomach or duodenum. This is much less common now with routine pharmacological prophylaxis. Endoscopy will confirm the diagnosis.

Treatment is angiographic embolization, with surgery a "salvage" option. But best is to prevent stress ulcer with prophylactic H2 blockers or PPIs, which is now common practice in the ICU setting.

> A 33-year-old man vomits a large amount of bright red blood.

There is not a lot of information here, but you can already define the territory where the bleeding is taking place: from the tip of the nose to the ligament of Treitz. To diagnose, don't forget to look at the mouth and nose, and then proceed with upper GI endoscopy.

> A 33-year-old man has had 3 large bowel movements that he explains all contained a lot of dark red blood. The last one was 20 minutes ago. He is diaphoretic and pale. Blood pressure is 90/70 mm Hg, and pulse is 110/min.

This is a challenging scenario, as the bleeding can be from anywhere in the GI tract. This patient seems to be actively bleeding, so the first diagnostic step is to examine the nose and mouth, then place an NG tube and aspirate.

Clinical Pearl

Rule of 2s in Meckel's diverticulum:

- Presents in 2% of the population
- Typically presents before age 2 years
- Occurs within 2 feet of the ileocecal valve
- Often has 2 types of mucosa (heterotopic gastric mucosa results in bleeding)

A 33-year-old man has had 3 large bowel movements that he explains all contained a lot of dark red blood. The last one was 20 minutes ago. He is diaphoretic and pale. Blood pressure is 90/70 mm Hg, and pulse is 110/min. A nasogastric tube returns copious amounts of bright red blood.

In this clinical case, diagnostic NG lavage has identified the source of bleeding as upper GI. Proceed with urgent endoscopy.

A 65-year-old man has had 3 large bowel movements that he explains all contained a lot of dark red blood. The last one was 20 minutes ago. He is diaphoretic and pale. Blood pressure is 90/70 mm Hg and pulse is 110/min. A nasogastric tube returns clear green fluid without blood.

If the NG tube had returned blood, the boundaries of bleeding would have been tip of the nose to ligament of Treitz. Clear fluid, without bile, would have excluded the area down to the pylorus, while aspirate with bile excludes down to the ligament of Treitz—provided you are sure the patient is bleeding now. That is the case here, so this patient is bleeding from somewhere distal to the ligament of Treitz. Further definition of the actual site is no longer within reach of upper endoscopy, and except for anoscopy looking for bleeding hemorrhoids, lower endoscopy is notoriously unrewarding during massive bleeding. If the bleeding is brisk (1 unit/4 hours), proceed with emergent angiogram for diagnosis and possible embolization; for slower bleeds, proceed with a tagged RBC scan.

A 72-year-old man has had 3 large bowel movements that he explains all contained a lot of dark red blood. The last one was 2 days ago. He is pale but has normal vital signs. A nasogastric tube returns clear green fluid without blood.

Note

Overall, 75% of all GI bleeding is upper, and virtually all causes of lower GI bleed are diseases of the elderly: diverticulosis, polyps, cancer, and angiodysplasias.

The clear aspirate is meaningless because the patient isn't bleeding right now. Thus, the guilty territory can still be anywhere from the tip of the nose to the anal canal.

- Diagnosis of a slow bleed or bleeding that has stopped is endoscopy (both upper and lower).
- Angiography is not the first choice. Even proponents of radionuclide studies don't have much hope of diagnosing if the patient last bled 3 days ago.

A 7-year-old boy passes a large bloody bowel movement.

In this age group, Meckel's diverticulum is the most likely etiology. Diagnose with radioactively labeled technetium scan.

A 41-year-old man has been in the ICU for 2 weeks with idiopathic hemorrhagic pancreatitis. He has had several percutaneous drainage procedures for pancreatic abscesses, chest tubes for pleural effusions, and bronchoscopies for atelectasis. He has been in and out of septic shock and respiratory failure several times. Ten minutes ago he vomited a large amount of bright red blood, and as you approach the bed he vomits another large amount of blood.

In the critical care setting, GI bleed is most likely due to a stress ulcer. This should have been prevented with H2 blockers and/or antacids, but once the bleeding occurs the diagnosis is made as usual with endoscopy. Treatment will be difficult. Start with endoscopic attempts (clipping, cautery), and consider angiographic embolization.

Acute Abdomen

Acute abdominal pain can be caused by perforation, obstruction, or inflammatory/ischemic processes. Physical exam reveals involuntary guarding, rigidity, or rebound tenderness.

- Acute abdominal pain caused by **perforation** has sudden onset and is constant, generalized, and very severe. The patient is reluctant to move and very protective of his abdomen. Except in the very old or very sick, impressive generalized signs of peritoneal irritation are found: tenderness, muscle guarding, rebound, and lack of bowel sounds. Free air under the diaphragm on upright x-rays confirms the diagnosis. Perforated peptic ulcer is the most common example. Emergency surgery is indicated.
- Acute abdominal pain caused by **obstruction** of a narrow duct (ureter, cystic, or common bile) has sudden onset of colicky pain, with typical location and radiation according to source. The patient moves constantly, seeking a position of comfort. There are few physical findings; they are limited to the area where the process is occurring.
- Acute abdominal pain caused by **inflammatory process** has gradual onset and slow buildup (at the very least a couple of hours; more commonly 6–12 hours). It is constant, starts as ill-defined and eventually localizes to the site of pathology, and often has typical radiation patterns. There are physical findings of peritoneal irritation in the affected area and (except for pancreatitis) systemic signs such as fever and leukocytosis. Ischemic processes affecting the bowel are the only ones that combine severe abdominal pain with blood in the lumen of the gut.

An acute abdomen mandates surgical exploration, with the exception of acute pancreatitis. Accordingly, etiologies that mimic an acute abdomen must always be considered prior to proceeding to surgery. These include myocardial ischemia (obtain an EKG), lower lobe pneumonia (perform a chest x-ray), and PE (suspect in an immobilized patient). Nonsurgical processes that mimic an acute abdomen should also be considered: pancreatitis (check serum amylase and lipase), urinary stones (perform a noncontrast CT of abdomen), and spontaneous bacterial peritonitis (SBP).

Acute pancreatitis should be suspected in the alcoholic who develops symptoms of an acute abdomen with epigastric pain. The classic presentation is progressive pain over a few hours (more rapid than other inflammatory processes) that is constant, epigastric, and radiates straight through to the back, with nausea, vomiting, and retching. Physical findings are relatively modest, but there may be vaguely localized discomfort in the epigastrium. Diagnose with serum amylase and lipase, and CT if the diagnosis is uncertain. Treatment is supportive therapy: NPO, NG suction, and IV fluids.

Biliary tract disease should be suspected in obese, multiparous women age 30–50 who present with right upper quadrant (RUQ) abdominal pain. While gallstones are more common in women than men, acute cholecystitis occurs with equal frequency. Acalculous acute cholecystitis is more common in older men and the critically ill.

Clinical Pearl

Exam questions (and real life) will use many descriptors to qualify the pain. These are essential in differentiating disease processes and should aid in selection of further diagnostic testing.

Clinical Pearl

Spontaneous bacterial peritonitis is a medical problem, not a surgical one. It should be considered in patients with ascites with mild generalized abdominal pain and fever. Diagnosis is made with paracentesis with fluid culture but is often empiric. Treatment is IV antibiotics.

Clinical Pearl

"Fat, female, forty, fertile" signifies the biliary etiology of abdominal pain.

Ureteral stones produce sudden onset colicky flank pain radiating to the inner thigh and scrotum or labia, sometimes with urinary symptoms like urgency and frequency, and with microhematuria discovered on urinalysis. Noncontrast CT is the best diagnostic test. Treatment most often involves analgesics and vigorous hydration to facilitate stone passage.

Acute diverticulitis is one of the few inflammatory processes that produces recurrent acute abdominal pain in the left lower quadrant (LLQ) (in women, the fallopian tube and ovary are other potential sources). Patients are typically middle-aged. Symptoms include fever and leukocytosis, with physical findings of peritoneal irritation in the LLQ and occasionally a palpable tender mass.

- CT with oral and IV contrast is diagnostic.
- Treatment is as follows:
  - NPO, IV fluids, and IV antibiotics
  - If there is evidence of perforation: emergency surgical exploration, with colectomy and diverting colostomy
  - If there is evidence of fistulization (most commonly to the bladder, presenting with **pneumaturia**): emergency surgical exploration with colectomy, fistula repair, and diverting colostomy
  - If there is no evidence of perforation or fistulization, but an abscess is identified: percutaneous drainage can often prevent the need for emergency surgical exploration and diverting colostomy
  - Whether or not emergency surgery is performed, colonoscopy is indicated ~6 weeks after an episode of diverticulitis to rule out underlying malignancy. The entire colon must be monitored for malignancy, so if a colectomy/colostomy is performed, endoscopy must evaluate the distal rectal stump as well as the intact colon.
  - Elective colon resection with primary anastomosis is indicated for patients who have had complications, multiple attacks, or continuing discomfort.

Note

If endoscopy is done in the presence of active inflammation, it increases the likelihood of iatrogenic perforation and decreases diagnostic sensitivity.

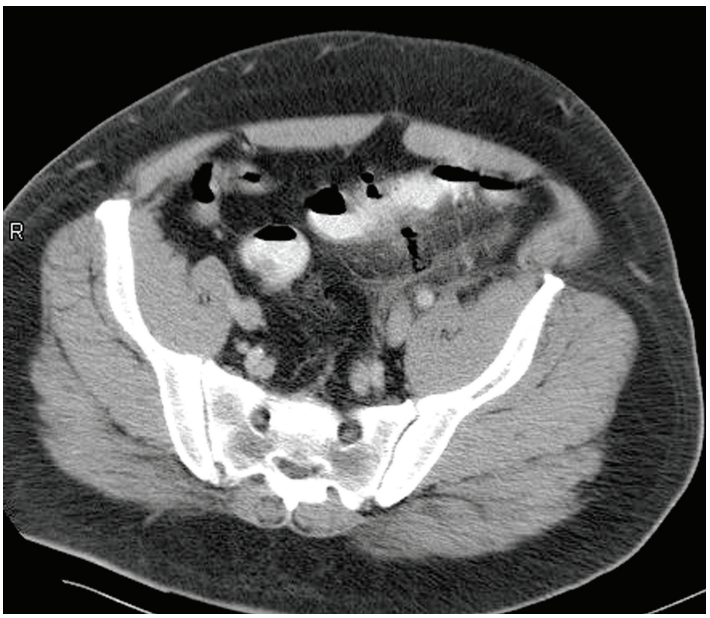


Figure 3-6. CT Scan Diverticulitis of Sigmoid Colon

Volvulus of the sigmoid (second most common cause of large bowel obstruction) is seen in the elderly. It presents with signs of intestinal obstruction and severe abdominal distention. X-ray is diagnostic, as it will show air-fluid levels in the small bowel, very distended colon, and a huge air-filled loop in the RUQ that tapers down toward the LLQ with the shape of a "bird's beak."

Treatment for an acute problem is proctosigmoidoscopy exam, which assesses for mucosal ischemia. Leaving a rectal tube in place allows for complete decompression and prevents immediate recurrence. Recurrent cases require elective sigmoid resection.

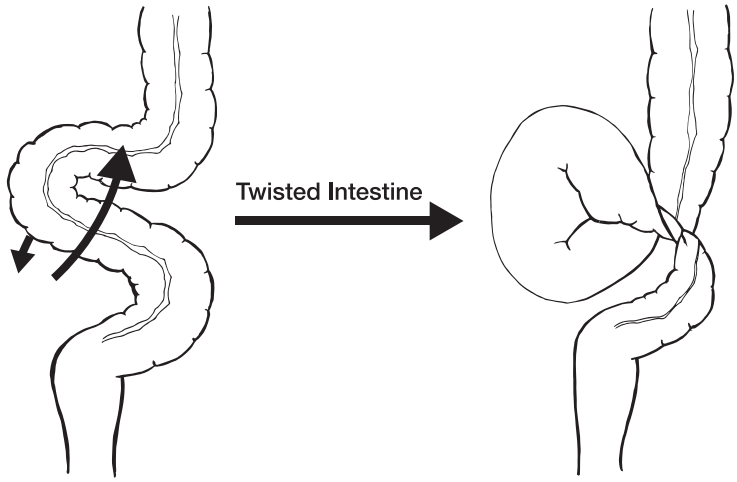


Figure 3-7. Volvulus of Sigmoid Colon

Mesenteric ischemia is seen in the elderly. The classic presentation (and examination scenario) is the development of an acute abdomen in someone with atrial fibrillation or recent MI: the source of the clot that breaks off and lodges in the superior mesenteric artery. Because the elderly do not mount impressive acute abdomens, the diagnosis often is made late, when there is blood in the bowel lumen (the only condition that mixes acute pain with GI bleeding) and lactic acidosis and sepsis have developed. In very early cases, arteriogram and embolectomy might save the situation, but once bowel ischemia is present surgical resection is mandatory. Early presentation will be pain out-of-proportion to the physical exam.

> A 59-year-old man arrives at the ED late at night with abdominal pain that began suddenly about an hour ago. The pain is now generalized, constant, and extremely severe. He lies motionless on the stretcher, is diaphoretic, and has shallow, rapid breathing. The abdomen is rigid, very tender to deep palpation, and has guarding and rebound tenderness in all quadrants.

This is clearly an acute abdomen. The short time elapsed and the circumstances attest to the severity and rapid onset of the problem, and the physical findings are impressive. This patient has generalized acute peritonitis. The best bet regarding its etiology is perforated peptic ulcer, but we do not need to prove that.

An acute abdomen does not need a precise diagnosis to proceed with surgical exploration. Myocardial infarction and pneumonia must be ruled out with EKG and chest x-ray, and it would be nice to have a plain x-ray or CT of the abdomen and a normal lipase. But the safest approach here is prompt emergency exploratory laparotomy.

Note

If a patient with a volvulus has an acute abdomen, he has a dead bowel.

> A 62-year-old man with cirrhosis and ascites presents with generalized abdominal pain that started 12 hours ago. He now has moderate tenderness over the entire abdomen, with some guarding and equivocal rebound. He has mild fever and leukocytosis.

Scenarios describing an acute abdomen in a cirrhotic patient should always raise concern for spontaneous bacterial peritonitis. A thorough evaluation for a surgical problem must be considered, but diagnosis is made via paracentesis.

> A 43-year-old man arrives at the ED with excruciating abdominal pain. He has a rigid abdomen, lies motionless on the examining table, has no bowel sounds, and is obviously in great pain, which he describes as constant. X-ray shows free air under the diaphragm.

An acute abdomen with pneumoperitoneum equals a perforated viscus. Emergency exploratory laparotomy is mandatory.

> A 44-year-old alcoholic presents with severe epigastric pain that began shortly after a heavy drinking episode. The patient reports the pain at 10/10 over a period of 2 hours. It is constant, radiates straight through to the back, and is accompanied by nausea, vomiting, and retching. Two years ago the patient had a similar episode that required hospitalization.

Abdominal pain in an alcoholic is suspicious for acute pancreatitis, especially when recurrent. Diagnosis is made with serum amylase and lipase. If the diagnosis is unclear or there is no improvement in a few days, CT may be necessary. Use caution with IV contrast, however, as alcoholic patients can be hypovolemic and prone to an acute kidney injury. Management is supportive therapy: NPO, NG suction, and IV fluids.

> A 43-year-old obese mother of 6 has severe right upper quadrant abdominal pain that began 6 hours ago. The pain was colicky at first, radiated to the right shoulder and around toward the back, and was accompanied by nausea and vomiting. For the past 2 hours the pain has been constant. Physical exam reveals tenderness to deep palpation, muscle guarding, and rebound in the right upper quadrant. Temperature is 38.3 C (101 F), and white blood cell count 16,000. The patient has a history of similar episodes of pain after eating fatty food, but they were all brief and resolved spontaneously or with anticholinergics.

The demographics should already raise suspicion of a biliary source of pain, and the remainder of the scenario is consistent with acute cholecystitis. Sonogram is the first choice for diagnosis. If equivocal, order a HIDA scan (radionuclide excretion scan). Medical management is first (antibiotics, NPO, IV fluids), but plan to do laparoscopic cholecystectomy during the same hospital admission to prevent recurrence or complications such as biliary pancreatitis.

> A 52-year-old man has right flank colicky pain of sudden onset that radiates to the inner thigh and scrotum. There is microscopic hematuria.

This scenario suggests ureteral colic; diagnosis is sometimes made with abdominal x-ray but typically requires a noncontrast CT.

> A 59-year-old woman has a history of 3 prior episodes of left lower quadrant abdominal pain, for which she was briefly hospitalized and treated with antibiotics. This patient began to feel discomfort 12 hours ago and now has constant left lower quadrant pain, tenderness, and a vaguely palpable mass. She has fever and leukocytosis.

LLQ pain suggests acute diverticulitis, especially when recurrent. Initial diagnosis is with CT scan, but a colonoscopy must be performed later to rule out an underlying colon cancer. Treat the acute attack medically (antibiotics, NPO), but elective sigmoid resection is advisable for recurrent disease. Percutaneous drainage is indicated if there is an abscess. If sepsis is present, emergency surgery (resection or colostomy) may be needed.

> An 82-year-old man develops severe abdominal distention, nausea, vomiting, and colicky abdominal pain. He has not passed any gas or stool for 12 hours and has a tympanitic abdomen with hyperactive bowel sounds. X-ray shows distended loops of small and large bowel. A very large gas shadow is located in the right upper quadrant and tapers toward the left lower quadrant with the shape of a bird's beak.

Clinical presentation and radiographic findings are diagnostic of sigmoid volvulus. Endoscopic intervention will relieve the obstruction. In recurrent cases, consider surgery. If the patient has an acute abdomen, it means the volvulus has progressed to bowel ischemia, and laparotomy is mandated.

> A 79-year-old man with atrial fibrillation develops an acute abdomen. No bowel sounds are audible. There is diffuse tenderness and mild rebound, with a trace of blood on rectal exam. He has acidosis and looks quite sick. X-ray shows a distended small bowel and distended colon up to the middle of the transverse colon.

An acute abdomen in an elderly person who has atrial fibrillation suggests embolic occlusion of the mesenteric vessels. Acidosis frequently ensues, and blood in the stool is often seen. Unfortunately, these signs usually mean significant ischemia is already present; however, if identified early, emergency embolectomy may prevent bowel infarction.

Hepatobiliary Disease

Liver

Primary hepatoma (hepatocellular carcinoma) is seen in patients with cirrhosis in the United States. Patients develop vague RUQ discomfort and weight loss. The specific blood marker is α-fetoprotein (AFP). CT will show location and extent. Resection is done if technically possible.

Metastatic cancer of the liver outnumbers primary cancer of the liver in the United States by 20:1. It is found by CT if follow-up for the treated primary tumor is underway or suspected due to rising carcinoembryonic antigen (CEA) in a patient with a history of colon cancer. If the primary is slow-growing and the metastases are confined to one lobe, resection can be done. Other treatment modes include radiofrequency ablation.

Hepatic adenoma may arise as a complication of birth control pills and is important because it can rupture and bleed massively inside the abdomen, presenting with diffuse abdominal pain, hypotension, and tachycardia. CT is diagnostic. Treatment if patients are symptomatic is to stop the oral contraceptives. Patients who present with hemorrhage should undergo transcatheter embolization, whereas signs of shock or evidence of rupture should be managed with emergency surgical exploration.

> A 53-year-old man with cirrhosis of the liver develops malaise, vague right upper quadrant abdominal discomfort, and a 20-pound weight loss. Physical examination shows a palpable mass that seems to arise from the left lobe of the liver. Alpha-fetoprotein is significantly elevated.

> A 53-year-old man develops vague right upper quadrant abdominal discomfort and a 20-pound weight loss. Physical examination shows a palpable liver with nodularity. Two years ago the patient had a right hemicolectomy for cancer of the ascending colon. His CEA had been within normal limits right after his hemicolectomy, but is now 10x the upper limit of normal.

Both vignettes are good descriptions of cancer in the liver, included to remind you that α-fetoprotein goes with primary hepatoma, whereas CEA goes with metastatic tumor from the colon.

- Management of both patients would start with a CT with contrast to define location and extent of the tumor.
- In the primary hepatoma, resection is done if a tumor-free anatomic segment can be left behind.
- In the metastatic tumor, resection is done if there are no other metastases, it is surgically possible, and the primary is relatively slow growing.

> A 24-year-old woman develops moderate, generalized abdominal pain of sudden onset, and shortly thereafter she faints. At the time of evaluation in the ED the patient is pale, tachycardic, and hypotensive. The abdomen is mildly distended and tender, and hemoglobin 7 g/dL. There is no history of trauma. She denies the possibility of being pregnant because she has been on birth control pills since age 14 and has never missed a dose.

This clinical picture is suspicious for bleeding from a ruptured hepatic adenoma secondary to birth control pills. It is pretty clear that the patient is bleeding into the abdomen, but CT will confirm this and probably show the liver adenoma as well. Surgery will follow. The patient must not take birth control pills in the future.

Pyogenic liver abscess is seen most often as a complication of biliary tract disease, particularly choledocholithiasis and acute ascending cholangitis. Patients develop fever, leukocytosis, and tenderness to palpation in the RUQ. U/S or CT is diagnostic. Percutaneous drainage is required.

Amoebic abscess of the liver (men > women 10:1) is generally seen in travelers from countries with endemic *Entamoeba histolytica* infection. Presentation and imaging diagnosis are similar to those for pyogenic liver abscesses, but amoebic abscess can be treated with metronidazole and rarely requires drainage. Definitive diagnosis is made by serology; because that test takes weeks to be reported, start empiric treatment immediately if amoebic liver abscess is clinically suspected. If improvement is seen, continue treatment; if not, drainage is indicated.

> A 29-year-old migrant worker from Mexico develops fever and leukocytosis, as well as tenderness over the liver when the area is percussed. He has mild jaundice and an elevated alkaline phosphatase. Sonogram of the right upper abdominal area shows a normal biliary tree and an abscess in the liver.

This scenario is suggestive of an amebic abscess, which is very common in Mexico. Alone among abscesses, these do not have to be drained, but can instead be effectively treated with metronidazole. Draw serology for amebic titers, but treat in the meantime as the results can take weeks.

> A 44-year-old woman is recovering from an episode of acute ascending cholangitis secondary to choledocholithiasis. She develops fever and leukocytosis and some tenderness in the right upper quadrant. A sonogram reveals a liver abscess.

This is fairly straightforward from a diagnosis perspective, but the issue is management: this is a pyogenic abscess and needs to be drained immediately. Drainage is typically done percutaneously by an interventional radiologist; otherwise laparoscopic or open drainage must be performed.

Clinical Pearl

If social history suggests an amebic abscess on the exam, don't be tempted by an answer choice that suggests aspirating the pus and sending it for culture. You cannot grow the ameba from the pus.

Jaundice

Jaundice is caused by elevated serum bilirubin (>5 mg/dL to cause clinically detectable changes in sclera or skin). It has 3 main etiologies:

- **Hemolytic jaundice**
  - Usually low level (bilirubin 6–8 mg/dL, but not 35–40)
  - All the elevated bilirubin is unconjugated (indirect)
  - No elevation of conjugated (direct) fraction
  - No bile in urine
  - Workup with peripheral blood smear, medication review, and possible bone marrow biopsy to determine etiology of hemolysis
- **Hepatocellular jaundice** (most common example: hepatitis)
  - Elevations of both fractions of bilirubin
  - High elevation of transaminases
  - Modest elevation of alkaline phosphatase
  - Workup with serologies to determine specific subtype

- **Obstructive jaundice**
  - Elevation of both fractions of bilirubin
  - Modest elevation of transaminases
  - High elevation of alkaline phosphatase
  - Workup with U/S looking for dilatation of the biliary ducts and for other clues about the nature of the obstructive process
  - In obstruction caused by **stones**, the stone that is obstructing the common duct may be seen, but stones are seen in the gallbladder, which cannot dilate because of chronic irritation.
    - Suspect obstructive jaundice caused by stones in obese, multiparous women age ≥45 who have high alkaline phosphatase, dilated ducts on sonogram, and non-dilated gallbladder full of stones.
    - The next step in that case is an endoscopic retrograde cholangiopancreatography (ERCP) to confirm the diagnosis. Then perform a sphincterotomy and remove the common duct stone. Cholecystectomy should usually follow during the same hospitalization. Also consider an intraoperative cholangiogram and a common bile duct exploration if not entirely cleared of residual stone.
  - In obstruction caused by a **tumor** (most commonly adenocarcinoma of the head of the pancreas, adenocarcinoma of the ampulla of Vater, or cholangiocarcinoma arising in the common duct itself):
    - Once the sonogram reveals a dilated gallbladder, thus raising suspicion of a tumor, the next diagnostic test should be CT scan. Pancreatic cancers that have produced obstructive jaundice are often big enough to be seen on CT. If CT is negative, ERCP is the next step.
    - Ampullary cancers or cancers of the common duct produce obstruction when they are very small, due to their location. Given their small size, they may not be seen on CT. Suspect ampullary cancer when jaundice coincides with anemia and positive blood in the stool. Endoscopy will show ampullary cancers, and cholangiography will show intrinsic tumors arising from the duct ("apple core") or small pancreatic cancers.
  - Workup with endoscopic U/S to identify and diagnose tumors in this region. Percutaneous biopsy is not indicated, as it could seed the abdominal wall with tumor. If cancer is suspected and a tumor is identified on CT or ERCP, it should be resected in patients without contraindications (i.e., evidence of metastatic disease).

Clinical Pearl

In malignant obstruction, a large, thin-walled, distended gallbladder may be palpable = Courvoisier-Terrier sign

Pancreatic cancer is aggressive and typically diagnosed at a relatively late stage. Early stage lesions are resectable by the Whipple procedure (pancreaticoduodenectomy). Ampullary cancer and cancer of the lower end of the common duct have a much better prognosis (about 40% cure).

> A 42-year-old woman presents with jaundice recently noted by her husband. She has total bilirubin 6 mg/dL, and labs report unconjugated, indirect bilirubin as 6 mg/dL and direct, conjugated bilirubin as 0. There is no bile in the urine, and she is otherwise asymptomatic.

On the exam, this vignette may have other features of hemolysis, but the lab studies alone are diagnostic of hemolytic jaundice. The challenge is figuring out why. Start with a complete medical history and physical exam.

A 19-year-old college student returns from a trip to Mexico and 2 weeks later develops malaise, weakness, and anorexia. On physical exam, he is notably jaundiced. Lab studies reveal total bilirubin 12 mg/dL, with 7 indirect and 5 direct. Alkaline phosphatase is mildly elevated, and transaminases are very high.

This scenario is consistent with hepatocellular jaundice, most likely infectious in nature. Obtain serologies to confirm diagnosis and type of hepatitis.

A 40-year-old obese mother of 5 presents with progressive jaundice, which she first noticed 4 weeks ago. She has total bilirubin 22 mg/dL, with 16 direct and 6 indirect, and minimally elevated transaminases. The alkaline phosphatase is 6 times the upper limit of normal. The patient gives a history of multiple episodes of colicky right upper quadrant abdominal pain brought about by ingestion of fatty food.

A classic history for gallstone disease, but now with jaundice. The elevated alkaline phosphatase is consistent with obstructive jaundice. Start with an U/S, which will likely show dilated intra- and possibly extrahepatic bile ducts and possibly visualize the culprit stone. ERCP is the next intervention to relieve the obstruction, and cholecystectomy will eventually have to be performed.

A 66-year-old man presents with progressive jaundice that he first noticed 6 weeks ago. He has total bilirubin 22 mg/dL, with 16 direct and 6 indirect, and minimally elevated transaminases. The alkaline phosphatase is about 6 times the upper limit of normal. He has lost 10 pounds in 2 months but is otherwise asymptomatic. Sonogram shows dilated intrahepatic ducts, dilated extrahepatic ducts, and a very distended, thin-walled gallbladder.

With similar lab findings to the previous case but with weight loss and a thin-walled gallbladder, this is worrisome for malignant obstructive jaundice. "Silent" obstructive jaundice is more likely to be caused by tumor, and a distended gallbladder is an ominous sign: when stones are the source of the problem, the gallbladder is thick-walled and nonpliable. The next step is CT of the abdomen to assess for a mass; if nondiagnostic, an ERCP would be indicated.

A 66-year-old man presents with progressive jaundice that he first noticed 6 weeks ago. He has a total bilirubin 22 mg/dL, with 16 direct and 6 indirect, and minimally elevated transaminases. Alkaline phosphatase is about 6 times the upper limit of normal. He is otherwise asymptomatic. Sonogram shows dilated intrahepatic ducts, dilated extrahepatic ducts, and a very distended, thin-walled gallbladder. CT shows dilated hepatic ducts but no mass. Endoscopic retrograde cholangiopancreatography reveals a narrow area in the distal common duct and a normal pancreatic duct.

Malignant obstruction of the biliary tree can be extrinsic (e.g., a mass of the head of the pancreas) or intrinsic, due to cholangiocarcinoma of the common bile duct, which this appears to be. This location is less likely to have a discrete mass visualized on CT scan. Brushings performed at the time of ERCP are diagnostic. Depending on the extent, malignant obstruction may be curable by pancreaticoduodenectomy (Whipple procedure).

A 64-year-old woman presents with progressive jaundice that she first noticed 2 weeks ago. Total bilirubin is 12 mg/dL, with 8 direct and 4 indirect, and minimally elevated transaminases. Alkaline phosphatase is about 10 times the upper limit of normal. She is otherwise asymptomatic but is found to be slightly anemic, with positive occult blood in the stool. Sonogram shows dilated intrahepatic ducts, dilated extrahepatic ducts, and a very distended, thin-walled gallbladder.

Another similar scenario with a subtle but important detail: GI bleeding. This again is suspicious for malignancy but suggests an ampullary carcinoma, which would bleed into the GI tract as well as obstructing the biliary tree. Endoscopic biopsy is diagnostic. If limited stage, ampullary carcinoma is also potentially curable via pancreaticoduodenectomy.

Gallbladder

Gallstones are responsible for the **vast majority of biliary tract pathology** (gallbladder and common duct). There is a spectrum of biliary disease caused by gallstones:

- The obese woman age 45 is the "textbook" victim.
- Incidence increases with age so that eventually rates are common across all ethnic groups.
- Asymptomatic gallstones are left alone. Historically, if another intra-abdominal operation were being performed, the gallbladder might have been simultaneously removed; these days, it is less commonly performed.

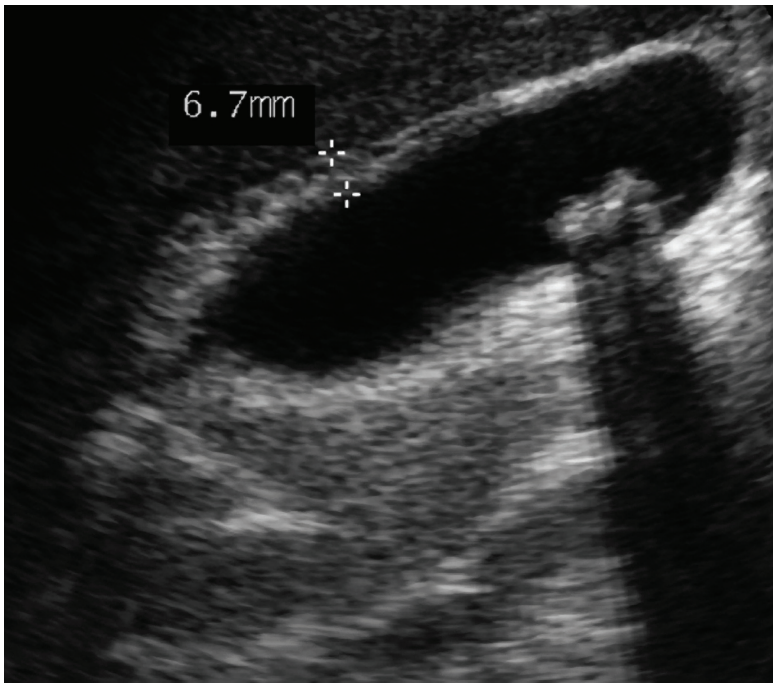


Figure 3-8. U/S Gallstones and Thickened Gallbladder Wall

Biliary colic is a typical pain pattern associated with cholelithiasis and/or chronic cholecystitis. It occurs when a stone temporarily occludes the cystic duct. The pain is described as colicky ("waves") in the RUQ radiating to the right shoulder and back, often triggered by ingestion of fatty food and accompanied by nausea and vomiting, but without signs of peritoneal irritation or systemic signs of inflammatory process. The episode is self-limited (typically <30 minutes) or is easily aborted by anticholinergics. RUQ U/S establishes diagnosis of gallstones, and elective laparoscopic cholecystectomy is indicated.

Acute cholecystitis starts as a biliary colic, but the stone remains at the cystic duct until an inflammatory process develops in the obstructed gallbladder.

- Pain becomes constant, modest fever and leukocytosis are present, and there are physical findings of peritoneal irritation in the RUQ.
- Liver function tests are minimally affected.
- U/S is diagnostic in most cases: gallstones, thick-walled gallbladder, and pericholecystic fluid.
- In equivocal cases, a radionuclide scan (HIDA) would show tracer uptake in the liver, common duct, and duodenum, but not in the occluded gallbladder.
- Management is initially with NPO, IV fluid, and antibiotics.
- Cholecystectomy is usually performed during the same hospital admission as an urgent case, though it is rarely a true emergency.
- Percutaneous cholecystostomy may be the best temporizing option in the very sick patient with a prohibitive surgical risk.

Acute ascending cholangitis is a far more morbid disease in which stones have reached the common duct, producing partial obstruction and ascending infection.

- Patients are often older and much sicker.
- Temperature spikes to 40.6 C (105 F), with chills and very high WBCs.
- There is typically mild hyperbilirubinemia, but the key finding is extremely high levels of alkaline phosphatase.
- **Charcot's triad**: fever, jaundice, and RUQ pain
- **Reynolds pentad**: Charcot's triad plus altered mental status and hypotension
- U/S demonstrates dilated ducts, but diagnosis is primarily clinical.
- IV antibiotics and emergency decompression of the common duct is lifesaving; this is performed ideally by ERCP, alternatively through the liver by percutaneous transhepatic cholangiogram (PTC), or rarely by surgery (common bile duct exploration).
- Eventually, cholecystectomy must be performed.

Biliary pancreatitis occurs when stones become impacted distally in the ampulla, temporarily obstructing both the pancreatic and biliary ducts. The stones often pass spontaneously, producing a mild and transitory episode of cholangitis along with the classic manifestations of pancreatitis (elevated amylase or lipase). U/S confirms gallstones in the gallbladder. Medical management (NPO, NG suction, IV fluids) usually leads to improvement, allowing elective cholecystectomy to be done later. If not, ERCP and sphincterotomy may be required to dislodge the impacted stone.

> A white, obese 40-year-old mother of 5 gives a history of repeated episodes of right upper quadrant abdominal pain brought about by the ingestion of fatty foods and relieved by the administration of anticholinergic medications. The pain is colicky, radiates to the right shoulder and around to the back, and is accompanied by nausea and occasional vomiting. Physical examination is unremarkable.

This is a classic scenario of gallstones causing biliary colic. Diagnose with U/S and treat with elective cholecystectomy.

> A 43-year-old obese mother of 6 has severe right upper quadrant abdominal pain that began 6 hours ago. The pain was colicky at first, radiated to the right shoulder and around toward the back, and was accompanied by nausea and vomiting. For the past 2 hours the pain has been constant. She has tenderness to deep palpation, muscle guarding, and rebound in the right upper quadrant. Her temperature is 38.3 C (101 F), and WBC count is 12,000. Liver function tests are normal.

Similar scenario, but now with pain, fever, and leukocytosis consistent with acute cholecystitis. Perform an U/S to confirm. The patient will need IV antibiotics followed by cholecystectomy.

> A 73-year-old obese mother of 6 has severe right upper quadrant abdominal pain that began 3 days ago. The pain was colicky at first but has been constant for the past 2.5 days. The patient has tenderness to deep palpation, muscle guarding, and rebound in the right upper quadrant. She has temperature spikes of 40–40.55 C (104–105 F), with chills. WBC count is 22,000, with a shift to the left. Labs include bilirubin 5 mg/dL and alkaline phosphatase 2,000 (~20 times normal).

This patient is much sicker than the previous one, with a higher fever and WBCs, along with abnormal liver function tests that appear concerning for acute ascending cholangitis. U/S will likely confirm dilated hepatic ducts, but this is a septic patient who needs several interventions: fluid resuscitation, IV antibiotics, and most importantly, emergency decompression of the biliary tract. This is accomplished preferentially with ERCP, but if unavailable or the patient is too sick, percutaneous transhepatic cholangiogram (PTC) is another option. Surgical decompression via exploration of the common bile duct is the last resort and rarely needed.

Pancreatic Disease

Acute pancreatitis is caused most commonly by alcohol abuse or gallstone obstruction. Epigastric and midabdominal pain starts after a heavy meal or bout of alcoholic intake, is constant, radiates straight through to the back, and is accompanied by nausea, vomiting, and continued retching even after the stomach is empty. There is tenderness and mild rebound in the upper abdomen. Serum amylase and lipase are elevated, and often serum hematocrit levels are high due to hypovolemia. Treatment is a few days of pancreatic rest (NPO, NG suction, IV fluids) and IV narcotics for severe pain, which is a common feature.

Acute severe pancreatitis is a much more morbid disease. It typically begins as an episode of acute pancreatitis but progresses to include pancreatic necrosis. The condition is accompanied by severe hypovolemia, marked leukocytosis, hyperglycemia, and hypocalcemia. Patients are quite ill and frequently require ICU admission and close monitoring, volume resuscitation, and mechanical ventilation. Nutrition is critical, ideally with post-pancreatic enteral access; TPN is a viable alternative.

Mortality is high and can be predicted by the Ranson criteria (the "prognosticators"):

- At admission:
  - Age >55
  - Glucose >200 mg/dL
  - WBC >16,000/dL
  - LDH >350
  - AST >250
- At 48 hours:
  - Hct drop >10% from admission
  - BUN increase >5 mg/dL from admission
  - Calcium <8 mg/dL
  - PaO_2 <60 mm Hg
  - Base deficit >4 mg/dL
  - Fluid resuscitation >6 L over 48 hours

Additional useful scoring systems include the APACHE (Acute Physiologic Assessment and Chronic Health Evaluation) and SOFA (Sequential Organ Failure Assessment) scores.

Pancreatic abscess (acute suppurative pancreatitis) may develop ~10 days after the onset of pancreatitis. Sepsis often ensues with fever and leukocytosis. CT will reveal fluid collection(s); management includes percutaneous drainage and imipenem or meropenem for the typical gram-negative bacterial infection. Open surgical drainage and debridement is often necessary for extensive abscess formation.

Pancreatic necrosis is another sequela of severe pancreatitis, and it can be notoriously difficult to manage. Although surgical necrosectomy is the best way to deal with necrotic pancreas, timing is crucial. Patients do far better by waiting at least 4 weeks before debridement of the dead pancreatic tissue if sepsis is not present. Hemorrhagic pancreatitis results when severe pancreatitis erodes into a vessel, resulting in anemia in addition to the above-mentioned problems. This is clinically recognized by Grey-Turner sign and Cullen sign, and diagnosed with CT scan.

Pancreatic pseudocyst can be a late sequela of acute pancreatitis or secondary to pancreatic trauma with unrecognized ductal injury. In either case, 4–6 weeks elapse between the original problem and the development of a pseudocyst. There is a collection of pancreatic fluid outside the pancreatic ducts, most commonly in the lesser sac, which can cause compressive symptoms on the stomach presenting as early satiety, vague discomfort, and occasionally a palpable mass. CT is diagnostic. Treatment is dictated by the size and age of the pseudocyst:

- Smaller cysts ≤6 cm or those present <6 weeks are not likely to have complications and can be observed for spontaneous resolution.
- Larger cysts (>6 cm) or those present >6 weeks are more likely to cause obstruction, bleed, or become infected. Treatment is required: internal drainage into the stomach via endoscopy or surgical cystogastrostomy, cystoduodenostomy, or cystojejunostomy.

Clinical Pearl

At admission, recall the Ranson criteria as **A**ge, **B**lood glucose, **C**ells (WBC), **D**ehydrogenase (LDH), and **E**nzymes (AST). At 48 hours, recall them as **A**rterial O_2, **B**ase deficit, **C**alcium, **D**rop in Hct, **E**levated BUN, **F**luids.

Chronic pancreatitis results from repeated episodes of pancreatitis (usually in alcoholics). Patients eventually develop calcified burned-out pancreas, steatorrhea, diabetes, and constant epigastric pain. The diabetes and steatorrhea can be controlled with insulin and pancreatic enzymes, but the pain is resistant to most modalities of therapy and can be incredibly debilitating. If ERCP shows specific points of obstruction and dilatation, operations that drain the pancreatic duct may help (e.g., Puestow procedure or lateral pancreaticojejunostomy).

> A 33-year-old alcoholic man presents in the ED with epigastric and midabdominal pain that began after eating a large meal 12 hours ago. The pain is constant and very severe and radiates straight through to the back. He vomited twice early on and continues to have episodes retching. He has tenderness and some muscle guarding in the upper abdomen, is afebrile, and has mild tachycardia. Serum lipase is 1,200 and hematocrit is 52%.

This is the classic presentation of alcohol-induced acute pancreatitis. Treatment is pancreatic rest: NPO, NG suction, IV fluids, analgesia.

> A 56-year-old alcoholic man presents with acute upper abdominal pain. The pain is constant, radiates straight through the back, and is extremely severe. He has serum amylase 800, hematocrit 40%, white blood cell count 18,000, blood glucose 150 mg/dL, and serum calcium 6.5. He is given IV fluids and kept NPO with nasogastric suction. By the next morning his hematocrit has dropped to 30%, serum calcium has remained below 7 despite calcium administration, and blood urea nitrogen (BUN) has gone up to 32. He has developed metabolic acidosis and a low arterial PaO_2.

Another scenario of acute alcoholic pancreatitis, but more severe than the previous one. At least 8 of the Ranson criteria are present in this patient, so predicted mortality is ~80%. Very intensive support will be needed. The common pathway to death is sepsis due to pancreatic abscess formation. Broad-spectrum antibiotics are mandatory; serial CT and early percutaneous drainage may be lifesaving. If there is radiographic evidence of pancreatic necrosis, surgical necrosectomy is indicated.

> A 57-year-old alcoholic is being treated for acute hemorrhagic pancreatitis. He was in the ICU for 1 week, requiring a chest tube for a pleural effusion and a respirator for several days, but eventually improved enough to be transferred to the floor. Two weeks after the onset of the disease he develops a fever spike and leukocytosis.

Even in the recovery phase of pancreatitis, an abscess can develop. Diagnose with CT scan, and treat with antibiotics and percutaneous drainage to start.

A 49-year-old alcoholic presents with acute pancreatitis but recovers and is discharged to rehabilitation. A month later he presents with upper abdominal discomfort and early satiety. On physical examination a large epigastric mass is identified deep within the abdomen.

A 55-year-old woman presents with vague upper abdominal discomfort, early satiety, and a palpable epigastric mass. Five weeks ago she was involved in a car accident in which she hit the upper abdomen against the steering wheel.

These are 2 presentations of pancreatic pseudocyst. You could diagnose it with a sonogram, but CT is probably the best choice.

- Small cysts (<6 cm) of brief duration (<6 weeks) can be watched for spontaneous resolution.
- Larger or older cysts could have serious complications (e.g., obstruction, infection, bleeding) and so require intervention.

Internal drainage via cystogastrostomy (surgical or endoscopic), cystoduodenostomy, or cystojejunostomy is the standard surgical treatment.

A disheveled, malnourished 62-year-old man presents to the ED requesting medication for pain. He smells of alcohol and complains bitterly of constant epigastric pain radiating straight through to the back, which he says he has had for several years. He has diabetes and steatorrhea. Abdominal x-ray demonstrates calcifications in the upper abdomen.

This scenario points to chronic pancreatitis, a very difficult problem to treat. Alcohol cessation is the first step, but diabetes management and pancreatic enzyme repletion are necessary. Pain control can be very challenging. Various operations can be performed to decompress the pancreatic duct depending on its anatomy, so if forced to select a diagnostic study, go with ERCP.

Hernias

All abdominal hernias should be electively repaired to avoid the risk of intestinal obstruction and strangulation. Exceptions include:

- Asymptomatic umbilical hernia in patients age <5 (they typically close spontaneously)
- Esophageal sliding hiatal hernias (not "true" hernias)

A hernia that becomes irreducible needs emergency surgery to prevent strangulation. If it has been irreducible for years, elective repair should be done.

Clinical Pearl

Not all incarcerated hernias are strangulated, but all strangulated hernias are incarcerated.

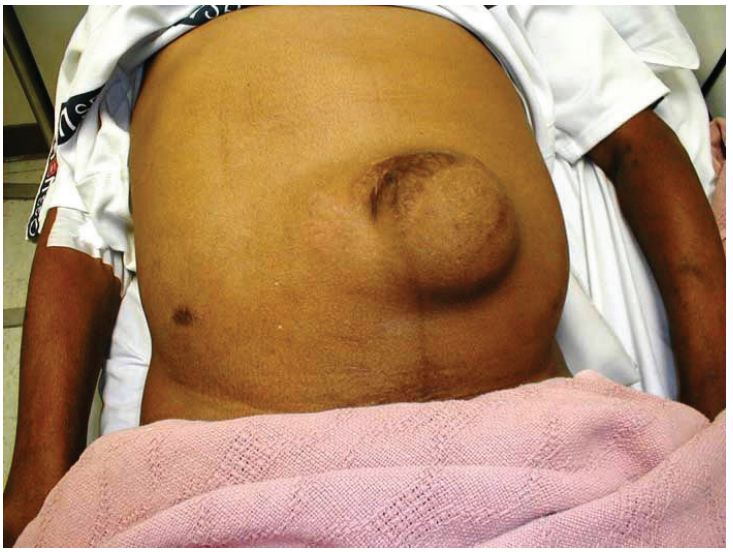


Figure 3-9. Large Umbilical Hernia (Gross Appearance)

A 9-month-old baby girl is brought in because she has an umbilical hernia. The defect is 1 cm in diameter, and the contents are freely reducible.

Elective surgical repair of hernias is generally recommended to prevent strangulation, but there are a few exceptions:

- Umbilical hernia in children age <5 may still close spontaneously, so observation alone is done if asymptomatic.
- Umbilical hernia in children at age 5 usually requires primary repair.

An 18-year-old man has a routine physical examination during college registration, during which time a right inguinal hernia is revealed. The external inguinal ring is about 2.5 cm in diameter, and a hernial bulge can be easily seen and felt going down into his scrotum when he is asked to strain. He is completely asymptomatic and was not even aware of the presence of the hernia.

Elective surgical repair is indicated. Even though the patient is asymptomatic, he should not be exposed to the risk of bowel incarceration or strangulation. The exam will not ask you about specific technical details, but this hernia is probably indirect. All routine unilateral first-time hernias can be repaired by an open or laparoscopic approach with a synthetic mesh. Laparoscopy is often favored for repair of recurrent inguinal, bilateral inguinal, and incisional hernias.

A 72-year-old farmer undergoes a physical examination required by his insurance company to be issued a life insurance policy. He has been healthy all his life and has "never been to the doctor." At the examination it is found that he has a large, left inguinal hernia that reaches down into the scrotum. Bowel sounds can be easily heard over it. The hernia is not reducible. He says that many years ago he used to be able to "push it back," but for the last 10–20 years he has not been able to do so.

This scenario describes a chronically incarcerated hernia: It cannot be reduced. An acutely incarcerated hernia and a strangulated hernia (i.e., blood flow has been compromised with evidence of bowel ischemia) are surgical emergencies. A chronically incarcerated hernia is less likely to progress to strangulation, and is therefore not an emergency; it should be repaired on a nonemergent basis.

BREAST

In all breast disease, cancer must be ruled out **even if the presentation initially suggests benign disease**. The only sure way to rule out cancer is to get tissue.

Risk factors for breast cancer include:

- Age
- Family history (a significant family history should raise concern for a BRCA genetic mutation and trigger appropriate testing)
- Early-age onset of menstruation
- Radiation exposure
- Later menopause
- Never having been pregnant

Diagnosis begins with physical exam followed by mammogram. Screening recommendations are as follows:

- Begin at age 50 or as early as age 40 if high risk.
- Women age <40 with significant risk factors should be screened with U/S and MRI if necessary. Stereotactic or U/S-guided core biopsy is the most convenient, effective, and inexpensive way to biopsy breast mass, whether it is palpable or is discovered by screening mammogram.

Fibroadenoma is primarily seen in young women (late teens to 30s) as a firm, rubbery mass that moves easily with palpation. Core biopsy is performed to establish diagnosis. Removal is optional in uncomplicated cases. Giant juvenile fibroadenoma is seen in very young adolescents, where it has very rapid growth; resection is indicated.

Cystosarcoma phyllodes tumor is most common in women in their 30s and 40s, but is seen in women of all ages. It can become very large and distort the entire breast, yet without invading or becoming fixed. Most tumors are benign, but a malignant variant is possible. Core biopsy is needed (FNA is not sufficient), and resection is mandatory due to the potential for malignant transformation.

Mammary dysplasia (fibrocystic disease, cystic mastitis) is most common in women of childbearing age but can affect women of any age. It often presents with bilateral tenderness related to the menstrual cycle and multiple lumps (cysts) that seem to come and go relative to the menstrual cycle. U/S can be used to evaluate breast complaints and is also diagnostic for simple cysts. Any dominant or persistent mass of concern should be worked up, including a mammogram and biopsy if appropriate.

Intraductal papilloma is the main etiology of bloody nipple discharge; however, do the following:

- Biopsy to rule out cancer
- Mammogram to exclude malignancy (but it may not demonstrate a papilloma, as it is small)
- Galactogram can help guide surgical resection
- Ultrasound to help diagnose; typically included in the routine evaluation of pathologic nipple discharge

Mastitis and **breast abscess** are commonly seen in lactating women; in nonlactating women, what appears to be a breast abscess is more likely cancer or hematoma due to trauma. Treatment for mastitis is oral antibiotics; treatment for true abscess is drainage via U/S-guided fine needle aspiration or incision and drainage.

Breast cancer should be suspected in any woman with a palpable breast mass. The index of suspicion increases with the patient's age. Other strong indicators of cancer include:

- Ill-defined fixed mass
- Retraction of overlying skin or recent retraction of the nipple
- Eczematoid lesions of the areola
- Reddish "orange peel" skin over the mass (peau d'orange), which is associated with inflammatory cancer caused by lymphatic involvement and resultant skin edema
- Palpable axillary nodes

A history of trauma does not rule out cancer.

Note

Breast cancer in pregnancy is diagnosed and treated in the same way as non-pregnancy, except that there is **no radiotherapy during the pregnancy** and **no chemotherapy during the first trimester**. Termination of the pregnancy is not necessary.

The radiologic appearance of breast cancer on mammogram includes an irregular, spiculated mass; asymmetric density; architectural distortion; or new microcalcifications.

Treatment of resectable breast cancer is as follows:

- Lumpectomy (partial mastectomy) plus post-op radiation **or** total mastectomy
- Either way, add simultaneous axillary sentinel lymph node sampling
  - Perform sentinel node biopsy only when nodes are not palpable on physical exam
  - If palpable, do a complete axillary lymphadenectomy
- Lumpectomy is ideal when tumor is small, not multicentric, and not associated with extensive DCIS

Infiltrating (or invasive) ductal carcinoma is the common, standard form of breast cancer. Other variants (lobular, medullary, tubular, mucinous) tend to have slightly better prognosis and are treated the same way as the standard infiltrating ductal. Lobular carcinoma has a higher incidence of bilaterality.

Inflammatory breast cancer is a clinical presentation of advanced breast cancer. It has a worse prognosis and is treated with chemotherapy prior to surgery. The surgery for inflammatory breast cancer is almost always a modified radical mastectomy. Inflammatory breast cancer is also one of the few instances where radiation is added following a total mastectomy.

Ductal carcinoma in situ (DCIS) may be a precursor to invasive breast cancer. Since it is confined to the ducts, it cannot metastasize (thus no axillary sampling is needed). Total mastectomy is recommended for multicentric lesions throughout the breast; many practitioners add a sentinel node biopsy in those patients in the event that invasive cancer is found following the mastectomy, as a sentinel node cannot be identified after the breast has been removed. Lumpectomy with or without radiation is used if the lesion(s) are confined to a limited portion of the breast.

Inoperable cancer of the breast is breast cancer that is not amenable to surgical resection. Inoperability is based primarily on local extent, not metastases. Treatment for inoperable breast cancer can include any combination of chemotherapy, hormonal therapy (if hormone-receptor positive), or radiation, and is often considered palliative. In some cases, chemotherapy may shrink the cancer, making surgical resection feasible.

Treatment after surgery is as follows:

- For tumors >1 cm, high-grade, HER2 positive, or positive axillary lymph nodes: adjuvant systemic therapy
- For tumors that are estrogen receptor-positive: antiestrogen hormonal therapy is an option
- For small, low-risk tumors: hormonal therapy without chemotherapy if tumors are estrogen-receptor positive; many decisions about adjuvant chemotherapy now also involve genomic analysis of the cancer

Premenopausal women receive tamoxifen, while postmenopausal women receive an aromatase inhibitor (e.g., anastrozole).

Persistent headache or back pain in women with a history of breast cancer suggests metastasis. MRI is diagnostic. Other tests for spine metastasis may include bone scan, CT scan, and PET scan. Brain metastases can be radiated or resected. The vertebral body and pedicles are the most common location in the spine. Recurrent metastatic breast cancer can also present with malignant pleural effusion; thoracentesis with cytological examination is indicated.

> An 18-year-old woman has a firm, rubbery mass in the left breast that moves easily with palpation.

This is most likely a fibroadenoma. The underlying concern for all breast masses is cancer, and the **best predictor of the likelihood of malignancy is age**.

- At age 18, the chances of malignancy are remote; begin with an U/S, which is diagnostic for fibroadenoma.
- At age 18 mammogram is not helpful.
- If a fibroadenoma is diagnosed, no intervention is necessary. For a lesion that appears more suspicious, a needle biopsy is necessary.

> A 14-year-old girl has a firm, movable, rubbery mass in her left breast that was first noticed 1 year ago and has since grown to be about 6 cm in diameter.

A breast mass this large in a young patient is characteristic of giant juvenile fibroadenoma. At age 14, chances of cancer are virtually zero. That avenue does not have to be explored, but the rapid growth requires resection to avoid cosmetic deformity.

> A 37-year-old woman has a 12×10×7 cm mass in her left breast. It has been present for 7 years and has slowly grown to its present size. The mass–firm, rubbery, completely movable–is not attached to chest wall or to overlying skin. There are no palpable axillary nodes.

The slow growth of this lesion suggests cystosarcoma phyllodes, a benign condition with the potential to transform into malignant sarcoma. After tissue diagnosis, proceed with resection.

A 35-year-old woman has a 10-year history of tenderness in both breasts related to her menstrual cycle, with multiple lumps on both breasts that seem to "come and go" at different times in the menstrual cycle. She now has a firm, round 2-cm mass that has not gone away for 6 weeks.

Note

Aspiration of fluid for symptom relief is not the same as fine needle aspiration (FNA) biopsy, which is aspiration of a solid mass to retrieve cells for diagnosis.

This presentation suggests a palpable cyst in fibrocystic disease (cystic mastitis, mammary dysplasia).

- Start with a mammogram to evaluate for any lesions suspicious for malignancy.
- U/S is also helpful in evaluating the persistent mass. Once U/S confirms the mass as a cyst, it can be aspirated for symptom relief. Otherwise, a simple cyst can be left alone.
  - If the mass goes away and the fluid aspirated is clear, no further testing is required.
  - If the fluid is bloody, it goes to cytology.
  - If the mass does not go away or recurs, a biopsy is required.

A 34-year-old woman has been experiencing bloody discharge from the right nipple intermittently for several months. There are no palpable masses and there is no family history of breast cancer.

This scenario is classic for an intraductal papilloma. Although cancer is a concern with bloody nipple discharge, benign intraductal papilloma is the most common cause of this complaint. First, cancer must be ruled out. Start with ultrasound, but mammogram is often also needed. Any intraductal mass should undergo core needle biopsy for diagnosis. Resect the duct and any identified intraductal lesion for symptomatic relief and definitive exclusion of a malignant etiology.

A 26-year-old lactating mother has cracks in the nipple and develops a fluctuating, red, hot, tender mass in the breast, along with fever and leukocytosis.

This is a typical example of a breast abscess, most likely to occur in breastfeeding women. Mammogram would be a low-yield diagnostic test: the patient's age and the presence of lactation put her at low risk for cancer. Drainage is the treatment for abscesses anywhere in the body, including the breast. U/S-guided percutaneous drainage is preferred in lactating women, since a formal incision and drainage carries a higher risk of developing a persistent milk fistula in the lactating breast.

A 49-year-old woman has a firm, 2-cm mass in the right breast that has been present for 3 months.

This could be anything and needs formal workup. Age is a strong determinant for risk of breast cancer. Suspect breast cancer on the exam if the patient is older; favor benign in a younger patient. Proceed with mammogram and often ultrasound to assess the palpable mass and to explore for other nonpalpable lesions; follow with a core needle biopsy.

A 34-year-old woman in month 5 of pregnancy reports a 3-cm firm, ill-defined mass in her right breast that has been present and growing for 3 months.

The diagnosis of possible breast cancer in the pregnant patient is done the same way as if she had not been pregnant. Mammogram is performed with fetal shielding, but more often it can be avoided with U/S-guided biopsy. Treatment is the same, except for no radiation during the pregnancy and no chemotherapy during the first trimester.

> A 69-year-old woman has a 4-cm hard mass with ill-defined borders in the right breast, movable from the chest wall but not movable within the breast. The skin overlying the mass is retracted and has an "orange peel" appearance.

> A 69-year-old woman has a 4-cm hard mass in the right breast under the nipple and areola with ill-defined borders, movable from the chest wall but not movable within the breast. The nipple became retracted 6 months ago.

> A 72-year-old woman has a red, swollen breast. The skin over the area looks like an orange peel. The area is not particularly tender, and it is debatable whether the area is hot or not. She has no fever or leukocytosis.

> A 62-year-old woman has an eczematoid lesion in the areola. It has been present for 3 months and looks to her like "some kind of skin condition" that has not improved or gone away with a variety of lotions and ointments.

These are all various presentations of breast cancer. The hard masses are likely invasive breast adenocarcinoma. The red, orange-peel skin is likely inflammatory breast cancer, and the eczematoid areolar lesion is likely Paget disease of the breast, a rare form of breast cancer. They all need mammograms and often ultrasound for further evaluation and multiple core biopsies of suspicious breast lesions, including biopsy of abnormal skin lesions when present.

> A 42-year-old woman hits her breast with a broom handle while doing housework. She noticed a lump in that area at the time, and 1 week later the lump is still there. She has a 3-cm, hard mass deep inside the affected breast and some superficial ecchymosis over the area.

This is a classic trap. It is cancer until proven otherwise. Trauma often brings the mass to the attention of the patient, but is not necessarily the cause of the lump. Proceed as with any other breast mass workup!

> A 58-year-old woman discovers a mass in her right axilla. She has a discrete, hard, movable, 2-cm mass. Physical examination of the breast is negative, and the patient has no enlarged lymph nodes elsewhere.

This is challenging, but it is another potential presentation for cancer of the breast. It could be lymphoma, but it could also be lymph node metastasis from another unrecognized primary cancer. A mammogram and ultrasound are needed to look for an occult primary

cancer in the breast, and the node must be biopsied (core needle biopsy or at least FNA may suffice). MRI of the breast is now in the workup for occult primary breast cancer, as well as for lobular cancers that cannot be fully visualized by mammogram or even U/S.

> A 60-year-old woman has a routine screening mammogram. The radiologist reports an irregular area of increased density, with fine microcalcifications that was not present 2 years ago on a previous mammogram.

On the exam, it is unlikely that you will be asked to read difficult x-rays, particularly mammograms, but you should recognize the description of a malignant radiologic image, which matches this description. Stick with the same algorithm and obtain tissue.

> A 44-year-old woman has a 2-cm palpable mass in the upper outer quadrant of her right breast. A core biopsy shows infiltrating ductal carcinoma. The mass is freely movable, and the breast is normal size. There are no other palpable lesions and no palpable axillary lymph nodes.

With a small tumor far away from the nipple, the standard option is partial mastectomy (lumpectomy) and sentinel lymph node biopsy. Even though no nodes are palpable, axillary sampling is necessary to assess for occult lymph node involvement, and possibly the need for adjuvant chemotherapy. Either way, adjuvant radiotherapy is indicated to augment the partial mastectomy and to prevent a local recurrence. If a total mastectomy is performed, radiotherapy is not typically necessary, except for large tumors (>5 cm) or axillary lymph node involvement.

> A 62-year-old woman has a 4-cm hard mass under the nipple and areola of her relatively small left breast. A core biopsy has diagnosed infiltrating ductal carcinoma. There are no palpable axillary nodes. The mammogram shows extensive associated branching calcifications thought to represent ductal carcinoma in situ (DCIS).

Lumpectomy is an ideal option when the tumor is small (in relation to the size of the breast), is located where most of the breast can be spared, and can be performed in a way that maintains the cosmetic appearance of the breast. A total mastectomy (also called simple mastectomy) is the choice here given the extent of disease. If necessary, a biopsy can be performed of the suspicious calcifications to confirm malignancy if there is any doubt. Axillary sampling of sentinel nodes at the time of breast surgery is also required (i.e., sentinel node biopsy if no palpable nodes).

> A 44-year-old woman has a 2-cm palpable mass in the upper outer quadrant of her right breast. A core biopsy shows lobular cancer.

> A 44-year-old woman has a 2-cm palpable mass in the upper outer quadrant of her right breast. A core biopsy shows medullary cancer of the breast.

Lobular cancer has a higher incidence of bilaterality; oftentimes, the extent of disease is not fully appreciated on mammogram and ultrasound (MRI may be helpful). It is treated much

in the same way as invasive ductal carcinoma. Many other variants of invasive cancer, e.g., medullary, tubular, have a somewhat better prognosis than infiltrating ductal, and they are all diagnosed and treated the same way.

> A 52-year-old woman has a suspicious area on mammogram. Multiple radiologically guided core biopsies show ductal carcinoma in situ.

Lumpectomy and radiation should be offered in cases of limited DCIS without the need for axillary sampling. If there are multicentric lesions all over the breast, total mastectomy (without radiation) is necessary. Sentinel node biopsy should be done at the time of mastectomy in the event that invasive carcinoma is found on the mastectomy pathology, since it is difficult to go back to do a sentinel node biopsy once the breast has been removed.

> A 44-year-old woman arrives at the ED because she is "bleeding from the breast." Physical examination shows a large ulcerated mass occupying the entire right breast and firmly attached to the chest wall. The patient maintains that the mass has been present for only "a few weeks," but a relative indicates that it has been there at least 2 years, maybe longer.

An all-too-frequent tragic case of neglect and denial, and perhaps psychiatric disorder. This is obviously an advanced breast cancer. Tissue diagnosis is still needed, along with either a core or incisional biopsy, but the main question here is what to do next. This cancer is inoperable, but palliation can be offered. Chemotherapy may be considered in the first line of treatment (or hormone therapy if the tumor is hormone-receptor positive), perhaps also radiation. In some cases the chemo- or hormone therapy will shrink the tumor enough to become operable for palliative surgery.

> A 37-year-old woman has a lumpectomy and axillary sentinel node biopsy for a 3-cm infiltrating ductal carcinoma. The pathologist reports clear surgical margins and metastatic cancer in 3 of the sentinel nodes that were removed. The tumor is positive for estrogen and progesterone receptors.

Very rarely is surgery alone sufficient to cure breast cancer. Most patients require subsequent adjuvant systemic therapy. The need for it is underscored by the finding of multiple involved axillary nodes. Chemotherapy is indicated here, followed by radiation (because she had a lumpectomy), and finally hormonal therapy, which, given her age, should be tamoxifen.

> A 66-year-old woman has a total mastectomy with sentinel lymph node biopsy for infiltrating ductal carcinoma of the breast. The pathologist reports that the tumor measures 1 cm in diameter and is estrogen receptor positive, with no lymph node involvement.

The adjuvant hormonal therapy of choice for postmenopausal women is an aromatase inhibitor (e.g., anastrozole), with chemotherapy as indicated. For very small, low-risk breast cancers like this one, typically in elderly women, hormone therapy without chemotherapy should be considered.

A 44-year-old woman presents with severe headaches for several weeks that have not responded to over-the-counter headache medication. She is 2 years post-op from modified radical mastectomy for T3N2M0 cancer of the breast, and she had several courses of post-op chemotherapy that she eventually discontinued because of the side effects.

This case is quite worrisome for recurrent metastatic disease. Despite the lack of metastases at initial presentation and adjuvant chemotherapy, this patient needs an immediate MRI of the brain and treatment as indicated.

A 39-year-old woman completed her last course of postoperative adjuvant chemotherapy for breast cancer 6 months ago. She comes to the clinic complaining of constant back pain for about 3 weeks. The patient is tender to palpation over 2 well-circumscribed areas in the thoracic and lumbar spine.

Clinical Pearl

Patients with metastatic bone lesions are at risk for pathological vertebral body fracture. If it occurs, treatment is orthopedic fixation.

Another presentation of metastatic breast cancer. These are bone metastases until proven otherwise. Again, use MRI or bone scan for diagnosis and treat with radiation and systemic therapy as indicated.

ENDOCRINE

Workup of thyroid nodules begins with thyroid function testing.

In **euthyroid patients**, nodules could be cancer, but the incidence is low and indiscriminate thyroidectomy is not justified. FNA is the diagnostic test of choice, especially with solitary nodule.

- If FNA reads as benign, continue to follow the patient but do not intervene.
- If FNA reads as malignant or indeterminate, follow with a thyroid lobectomy. In indeterminate cases, intraoperative frozen section is necessary to guide extent of resection.
- A total thyroidectomy should be performed in follicular cancers so radioactive iodine can be used in the future if needed to treat blood-borne metastases.

In **hyperthyroid patients**, nodules are almost never cancer, but they may be the source of the hyperfunction ("hot adenomas").

- Clinical signs of hyperthyroidism include weight loss, palpitations, heat intolerance, moist skin, hyperactive behavior, and tachycardia including atrial fibrillation or flutter.
- Lab confirmation includes a high T4 and low TSH.
- Nuclear scan will show whether the nodule is the source.
- Treatment is usually radioactive iodine, but those with a "hot adenoma" have the option of surgical excision of the affected lobe.

Hyperparathyroidism classically presents with "stones, bones, abdominal groans, and psychiatric moans," but in reality it is most commonly discovered incidentally when routine bloodwork turns up high serum calcium.

- Step 1 is to repeat the calcium level, check phosphorus, and rule out cancer with bone metastases.
- If findings persist, do parathyroid hormone (PTH) determination and interpret in light of serum calcium.

- Around 20% of asymptomatic patients become symptomatic, so elective intervention is justified.
- Around 90% of patients with hyperparathyroidism have a single adenoma. Resection is curative, and preoperative localization with a sestamibi radionuclide scan is crucial to localize the culprit gland.
- Pre- and intraoperative hormone testing confirms successful resection.
- Glandular hyperplasia is the second most common etiology.

Cushing syndrome is the constellation of clinical signs that accompany elevated cortisol: fat deposits in the face, a ruddy complexion, hirsutism, interscapular fat ("buffalo hump"), truncal obesity with abdominal striae, and thin weak extremities, classically in a patient with a previously normal appearance. Osteoporosis, diabetes, hypertension, and mood changes may be present. Workup starts with an overnight low-dose dexamethasone suppression test.

- Cortisol suppression at low dosage will rule out the disease.
- If no suppression, measure 24-hour urine-free cortisol; if elevated, move to a high-dose suppression test.
  - Suppression at a higher dose identifies pituitary microadenoma (Cushing disease).
  - No suppression at higher dose identifies adrenal adenoma (or a paraneoplastic syndrome).
- Do appropriate imaging studies (MRI for pituitary, CT for adrenal), and surgically remove the offending adenoma.
- Don't forget the most common etiology: iatrogenic, from exogenous steroid administration.

Zollinger-Ellison syndrome (gastrinoma) presents as virulent PUD, resistant to usual therapy (acid suppression, *H. pylori* eradication) and more extensive than usual (multiple and more extensive ulcers). Some patients also have watery diarrhea. Measure gastrin and do a secretin test; if values are equivocal, locate the tumor with CT (with contrast) of the pancreas and treat with surgical resection. Omeprazole helps those with metastatic disease.

Insulinoma produces CNS symptoms because of low blood sugar, always when the patient is fasting. Differential diagnosis is with reactive hypoglycemia (attacks occur after eating) and self-administration of insulin. In the latter, the patient has reason to be familiar with insulin (some connection with the medical profession or with a diabetic patient), and in plasma assays the patient has high insulin but low C-peptide. In insulinoma, both are high. Do a CT with contrast of the abdomen to locate the tumor and then surgically resect.

Glucagonoma produces severe migratory necrolytic dermatitis, resistant to all forms of therapy, in a patient with mild diabetes, mild anemia, glossitis, and stomatitis. Glucagon assay is diagnostic; CT is used to locate the tumor. Surgical resection is curative. Somatostatin and streptozocin have a modest response for patients with metastatic or inoperable disease.

> A 62-year-old woman is applying her makeup when she notices a lump in the lower part of the neck, visible when she swallows. Physical examination identifies a prominent, 2-cm mass on the left lobe of the thyroid plus 2 small masses on the right lobe. They are all soft, and she has no palpable lymph nodes in the neck.

Most thyroid nodules are benign. Surgical removal to ascertain the diagnosis is not recommended, but evaluation is necessary. Worrisome features: young patient, male gender, single

nodule, history of radiation to the neck, solid mass on sonogram, and cold nodule on scan. FNA is diagnostic.

> A 21-year-old man is found on a routine physical examination to have a single, 2-cm nodule in the thyroid gland. His thyroid function tests are normal. A fine needle aspiration is read as indeterminate.

Surgery is indicated for a thyroid mass with a malignant FNA and those that are indeterminate.

> A 32-year-old woman is undergoing a thyroid lobectomy for a 2-cm mass that had been reported on fine needle aspiration as a "follicular neoplasm, not otherwise specified." Frozen section in the operating room is consistent with follicular cancer.

This is a commonly tested scenario. Complete total thyroidectomy should be performed.

> Blood chemistry done during a routine examination indicates that an asymptomatic patient has a serum calcium 12 mg/dL. Repeat testing is 11.6 mg/dL. Serum phosphorus is low.

Hypercalcemia with hypophosphatemia raises suspicion for a parathyroid adenoma.

- Classically, hypercalcemia presents with kidney stones, abdominal pain, or psychiatric symptoms that prompt checking serum calcium level.
- In reality, hypercalcemia is usually noted incidentally on routine labs.
- Although most cases of hypercalcemia are caused by metastatic cancer, that scenario is less likely in an asymptomatic patient who would also likely have a normal phosphorus level.
- The next diagnostic test is serum parathyroid hormone level, then a sestamibi nuclear scan to localize the adenoma. Once localized, surgical resection is indicated.

> A 32-year-old woman is admitted to the psychiatry unit after being found wandering around the park in her underwear. Vital signs are significant for blood pressure 180/110 mm Hg and blood glucose 225 mg/dL. On physical exam, facial hair and central obesity are noted. Her driver's license photo from 2 years ago shows a much thinner face without hair.

This scenario describes a case of Cushing syndrome. On the exam you may be shown photos. Start with the overnight low-dose dexamethasone suppression test:

- If the patient suppresses at a low dose, she does not have the disease.
- If she does not suppress at a low dose, verify that 24-hour urine-free cortisol is elevated; then go to high-dose suppression testing.
  - If the patient suppresses at a high dose, get an MRI of the head looking for the pituitary microadenoma, which should be removed by the transnasal, transsphenoidal route.
  - If she does not suppress at a high dose, do a CT or MRI of the adrenal glands looking for an adenoma there.

A 28-year-old woman has virulent peptic ulcer disease. Extensive medical management including eradication of *H. pylori* fails to heal her ulcers, which on endoscopy are present in the first and second portions of the duodenum.

Uncontrollable and extensive PUD is suspicious for gastrinoma (Zollinger-Ellison syndrome). Start by measuring serum gastrin. If the value is not clearly normal or abnormal, a secretin stimulation test is helpful. CT of the abdomen with IV and oral contrast will help localize for surgical planning.

A second-year medical student is hospitalized after collapsing on the ward with a seizure. Blood glucose is markedly low. Serum testing reveals a low level of C-peptide.

High insulin with low C-peptide is diagnostic of exogenous insulin administration, especially when the patient is a healthcare provider. Proceed with psychiatric evaluation and counseling. If C-peptide was normal, work up for an insulinoma with CT of the abdomen with IV and oral contrast followed by surgical resection.

A 48-year-old woman has had severe, migratory dermatitis for several years, unresponsive to multiple topical creams. She is thin and has mild diabetes mellitus.

Diabetes with severe dermatitis is suspicious for a glucagonoma. To diagnose, measure serum glucagon level. CT of the abdomen with IV and oral contrast will help localize and plan surgical resection. If inoperable, use somatostatin to control symptoms and streptozocin as the indicated chemotherapeutic agent.

Primary hyperaldosteronism can be caused by an adenoma or by hyperplasia of the adrenal cortex. In either case, the key finding is hypokalemia in a hypertensive patient (usually female) who is not on diuretics.

- Sustained hypertension
- Modest hypernatremia
- Metabolic alkalosis
- High aldosterone
- Low renin

Appropriate response to postural changes (more aldosterone when upright than when lying down) suggests glandular hyperplasia (idiopathic form, which is treated medically), whereas lack of response or inappropriate response is likely secondary to an adrenal adenoma. Adrenal CT scan will localize the lesion, and surgical excision is curative. This is **sustained surgical hypertension**.

Pheochromocytoma is seen in thin, hyperactive women who have attacks of pounding headache, perspiration, palpitations, and pallor, due to extremely high but paroxysmal BP elevations. By the time patients are seen, the attack has subsided and BP may be normal, leading to a frustrating lack of diagnosis.

Clinical Pearl

- Pheochromocytoma is known as a "10% tumor": 10% are familial, 10% are extra-adrenal, 10% are bilateral, 10% are malignant, and 10% occur in children.
- Recent literature has revealed lower rates of these findings, but this is still a testable principle on the exam.

Start the workup with a 24-hour urinary metanephrines level (previously utilized urinary VMA is less sensitive). Follow with a CT of the abdomen and pelvis; if CT is negative, a radionuclide study may be necessary to identify an extra-adrenal tumor.

Treatment is surgical resection following preoperative alpha blockade. Meticulous anesthesia management and hemodynamic monitoring are needed to avoid a hypertensive crisis. This is **paroxysmal hypertension**.

Renovascular hypertension (secondary hyperaldosteronism) is seen in 2 populations:

- Young women with fibromuscular dysplasia
- Old men with atherosclerotic disease

Clinical Pearl

The organ of Zuckerkandl is the location of the chromaffin cells at the bifurcation of the abdominal aorta. It is a commonly quizzed site of extra-adrenal pheochromocytoma.

This is sustained surgical hypertension and secondary hyperaldosteronism. In both groups, hypertension is resistant to the usual medications, and a telltale faint bruit over the flank or upper abdomen suggests the diagnosis. Diagnostic testing begins with duplex U/S of the renal vessels followed by CT angiogram for anatomical characterization and intervention planning. Treatment is endovascular balloon dilation and stenting.

> A 45-year-old woman presents for an annual checkup. She is found to be hypertensive, although her blood pressure was normal on her previous exam. Lab studies show serum sodium 144 mEq/L, serum bicarbonate 28 mEq/L, and serum potassium concentration 2.1 mEq/L. She takes no medications.

This constellation is typical for hyperaldosteronism, possibly due to an adenoma. Measure serum aldosterone and renin levels, and if confirmatory (aldosterone high, renin low), proceed with determinations lying down and sitting up. Adrenal hyperplasia (appropriate response to postural changes) is managed medically with spironolactone, whereas adrenal adenoma (no response or minimal response to postural changes) is managed by surgical resection.

> A thin, 38-year-old woman presents with complaints of intermittent, severe headaches associated with palpitations and perspiration. Upon examination she is in no distress. Vital signs are normal, and she has no headache currently. Routine bloodwork is normal.

Not a lot of information is given, but the case is suspicious for pheochromocytoma. Start with a 24-hour urinary metanephrine exam. If elevated, proceed with CT of the abdomen and pelvis. Surgery following alpha blockade is curative. Ask about family members with similar symptoms. If CT is not diagnostic but clinical suspicion is high, consider an extra-adrenal site.

> A 33-year-old woman presents for a checkup and is found to have blood pressure 160/90 mm Hg. Six months ago she was found to be hypertensive and was started on 2 antihypertensive medications. On physical exam today a bruit is audible during auscultation of the abdomen.

Even with the physical exam findings alone, this scenario is suspicious for renovascular hypertension due to fibromuscular dysplasia. Start with a duplex U/S followed by CT angiogram, and treat endovascularly with dilation and stenting. Most patients can be taken off their antihypertensive medications.

SKIN

Cancer of the skin is typically seen in fair-skinned people with significant sun exposure. The 3 most common types of skin cancer are basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and melanoma.

Initial diagnosis is made by biopsy (shave, punch, or excisional). Skin cancers are notorious for having multiple locations over the course of a lifetime.

BCC (>50% of cases) presents as a raised waxy lesion or a nonhealing ulcer, often in the upper part of the face (above the lips). BCC does not metastasize, but it can continue to grow with relentless local invasion ("rodent ulcer"). Treatment is excision with negative margins (1 mm is enough).

SCC (>25% of cases) presents as a nonhealing ulcer, often in the lower part of the face. It does metastasize to local lymph nodes. Excision with wider margins is necessary (4–6 cm), and lymph node dissection may be indicated for very large/deep lesions or for those with enlarged/palpable nodes. Radiation is an option for unresectable lesions, as well adjuvant therapy for advanced lesions.

Melanoma is an aggressive malignancy that usually originates in a pigmented lesion. Suspect any lesion with the ABCD characteristics:

- Asymmetric (A)
- Has irregular borders (B)
- Contains different colors (C)
- Diameter (D) >0.5 cm

Also suspect melanoma in a pigmented lesion (dysplastic nevus) that has changed in any way (grows, ulcerates/bleeds, changes color/shape). Biopsy reports for melanoma must report both the diagnosis and thickness and depth of invasion, as the diagnosis/management are directly related to those factors.

If palpable nodes are present, treatment is surgical excision with lymphadenectomy. If nodes are not palpable, treatment is sentinel lymph node biopsy. Margins and prognosis are as follows:

- **Melanoma in situ (noninvasive melanoma)**: excellent prognosis and requires local excision with 5 mm margins
- **Lesions <1 mm**: require local excision with 1 cm margins; good prognosis
- **Lesions 1–2 mm**: require resection with 1–2 cm margins; worse prognosis
- **Lesions >2 mm**: require excision with wide margins 2 cm; poor prognosis

Melanoma can metastasize anywhere in the body and at any time from a previous occurrence. Ipilimumab (a monoclonal antibody) and other newer agents have emerged as standard options for adjuvant therapy for high-risk melanoma.

> A 65-year-old farmer presents with an indolent, raised 1.2-cm skin mass over the bridge of the nose that has been slowly growing over the past 3 years. There are no enlarged lymph nodes in the head and neck.

BCC can present as a waxy raised lesion or a "punched-out" ulcer. Both, however, have a preference for the upper part of the face. Diagnosis is made with full-thickness biopsy at the edge of the lesion (shave or punch) or complete excision with a narrow margin of uninvolved skin. Treatment is surgical excision with negative margins but conservative width.

Clinical Pearl

Melanoma is highly unpredictable. If the patient has a history of melanoma, any new tumor regardless of location should raise suspicion for recurrent metastatic melanoma.

A blond 69-year-old retired Navy sailor has a nonhealing 1.5-cm ulcer on the lower lip that has been slowly enlarging for the past 8 months. He is a pipe smoker, and he has no other lesions or physical findings.

This scenario is more suspicious for SCC based on location, but diagnosis is similarly made with a shave or punch biopsy. Manage with surgical resection with a wider (1 cm) margin (≥1 cm). Complex surgical reconstruction may be needed based on location and extent of resection.

A redheaded, freckled, 23-year-old woman who routinely tans presents to her physician after noticing a skin lesion on her shoulder. It is 1.8 cm, pigmented, and asymmetric, with irregular borders.

Although this patient is young, her complexion and habits put her at higher risk for skin cancer, and the characteristics are highly concerning for malignancy. Diagnosis is made by excisional biopsy, and a narrow margin is preferred. Once diagnosis is confirmed, definitive treatment is wide local excision with margins based on depth of invasion. Sentinel lymph node biopsy is indicated for lesions >1 mm thickness or lesions >0.75 mm with high risk features such as ulceration or high-mitotic rates.

A 44-year-old man presents with abdominal pain and is sent for CT scan. He is found to have multiple hepatic masses, but no other abdominal masses are identified. His medical history includes a toe amputation at age 18 for a "black tumor" under the toenail.

A 66-year-old man presents with an upper gastrointestinal bleed and is found to have a duodenal mass. His past medical history includes right eye enucleation for a "tumor" several years ago.

Melanoma is notorious for recurring at unpredictable intervals and in unusual locations. Suspect metastatic melanoma in these scenarios. An isolated tumor (e.g., duodenal) can be treated with surgical resection, whereas multiple sites or unresectable lesions should be treated medically with systemic therapy, e.g., immunotherapy.

UROLOGIC

Urologic Emergencies

Testicular torsion is seen in adolescent boys. This is one of the few urologic emergencies.

- There is very severe testicular pain of sudden onset, but no fever, pyuria, or history of recent mumps.
- The testis is swollen, exquisitely tender, "high riding," and with a "horizontal lie."
- The cord is not tender (differs from acute epididymitis).

- U/S may be performed at the bedside, but time is critical and care should not be delayed to obtain a formal U/S. Immediate surgical intervention is indicated: detorsion and bilateral orchiopexy.

Acute epididymitis can be confused with testicular torsion. It is seen in young men old enough to be sexually active.

- There is severe testicular pain of sudden onset, fever, and pyuria.
- The testis is swollen and very tender, but in a normal position.
- The cord is very tender.
- Treatment is antibiotics, but U/S is typically performed to avoid missing a possible diagnosis of testicular torsion.

The combination of **obstruction and infection of the urinary tract** is the other condition that is a urologic emergency. Any situation in which these two conditions coexist can lead to destruction of the kidney in a few hours, and potentially to death from sepsis. A typical scenario is a patient who is being allowed to pass a ureteral stone spontaneously, and who suddenly develops fever, chills, and flank pain. In addition to IV antibiotics, immediate decompression of the urinary tract above the obstruction is required. This should be accomplished by the quickest and simplest means, i.e. ureteral stent or percutaneous nephrostomy.

UTI (cystitis) is very common in women of reproductive age and requires no elaborate workup. Patients have frequent, painful urination, with small volumes of cloudy and malodorous urine. Empiric antimicrobial therapy is used. More serious infections such as pyelonephritis, as well as a UTI in children or young men, require urinary cultures and a urologic workup to rule out concomitant obstruction as the reason for the serious infection. Urinary cultures are also indicated in women with frequent/recurrent UTI.

Pyelonephritis, an infection involving the kidney, produces chills, high fever, nausea and vomiting, and flank pain. IV antibiotics (guided by cultures) and urologic workup (intravenous pyelogram [IVP] or sonogram to assess for anatomic abnormalities) are required.

Acute bacterial prostatitis is seen in older men who have chills, fever, dysuria, urinary frequency, diffuse low back pain, and an exquisitely tender prostate on rectal exam. IV antibiotics are indicated. Further rectal examination should not be performed.

> A 14-year-old boy presents in the ED with very severe pain of sudden onset in his right testicle. There is no fever, pyuria, or history of recent mumps. The testis is swollen and exquisitely painful, but the cord is not tender.

This is testicular torsion—a urological emergency. Do not waste time on imaging, proceed to the OR for surgical detorsion and bilateral orchiopexy.

> A 24-year-old man presents in the ED with very severe pain of recent onset in his right scrotum. He is febrile to 39.4 C (103 F), with pyuria. The testis is in the normal position, but it is swollen and exquisitely painful. The cord is also very tender.

This describes an infectious problem, and with a tender cord this is most concerning for acute epididymitis. This is not a surgical emergency like testicular torsion, but is managed medically with antibiotics. Get an U/S to confirm no torsion is present.

A 72-year-old man is being observed with a ureteral stone that is expected to pass spontaneously. He develops fever to 40 C (104 F) and flank pain.

Obstruction and infection of the urinary tract is a dangerous combination. IV antibiotics are required, but the obstruction must also be relieved immediately. Stone extraction would be hazardous, so the option in addition to antibiotics would be decompression by ureteral stent or percutaneous nephrostomy.

A 49-year-old woman presents with 5 days of frequent, painful urination, with small volumes of cloudy and malodorous urine. For the first 3 days she had no fever, but for the past 2 days she has been having chills, high fever, nausea, and vomiting. She has also had pain in the right flank in the past 2 days.

The natural history of infections of the urinary tract is ascending, ultimately leading to pyelonephritis. UTI should not occur in men or in children, and thus should trigger a workup looking for a cause. Women of reproductive age, on the other hand, get cystitis all the time, and they are treated with appropriate antibiotics without great fuss. However, when they get flank pain and septic signs it's much more serious. This woman needs hospitalization, IV antibiotics, and at least a sonogram to make sure that there is no evidence of urinary tract obstruction.

A 72-year-old man presents with chills, fever, dysuria, urinary frequency, diffuse low back pain, and an exquisitely tender prostate on rectal exam.

Acute bacterial prostatitis presents in this manner, and is treated with IV antibiotics. Do not perform any more rectal exams or any vigorous prostatic massage, as this could lead to septic shock.

A 33-year-old man has urgency, frequency, and burning pain with urination. The urine is cloudy and malodorous. He has mild fever. On physical examination the prostate is not warm, boggy, or tender.

The first part of this vignette sounds like prostatitis, which would be common and not particularly challenging; however, if the prostate is normal on examination, things become less clear. The point of the vignette is that men—particularly young men—rarely get UTI.

This infection needs to be treated, so check urinary cultures and start antibiotics, but also start a urologic workup. Do not start with cystoscopy (as to not instrument an infected bladder; you could trigger septic shock); start with an U/S.

Retention and Incontinence

Urinary retention is a common problem and often tested on the exam. Take into consideration the patient and circumstances when evaluating and managing.

Acute urinary retention is very common in men, secondary to benign prostatic hypertrophy. It is often precipitated during a viral illness, use of antihistamines, and abundant fluid intake. The

patient wants to void but cannot, and the markedly distended bladder is palpable. Treatment is an indwelling catheter for ≥3 days, with alpha-blockers and 5-alpha-reductase inhibitors.

Postoperative urinary retention is common and sometimes masquerades as incontinence. The patient may not feel the need to void because of post-op pain and medications, but will report that every few minutes there is involuntary release of small amounts of urine. A distended bladder is palpable on exam and visible on bladder scanning, confirming that the problem is overflow incontinence from retention. Manage with an indwelling bladder catheter.

Stress incontinence is common in middle-aged women who have had many pregnancies and vaginal deliveries. They leak small amounts of urine whenever intra-abdominal pressure suddenly increases, as with sneezing, laughing, or lifting a heavy object. They do not have any incontinence during the night. Examination will show a weak pelvic floor, with the prolapsed bladder neck outside of the "high-pressure" abdominal area.

For early cases, pelvic floor exercises (Kegel) may be sufficient; for more advanced cases or those with cystoceles, surgical reconstruction of the pelvic floor may be necessary.

> A 60-year-old man arrives at the ED because he has not been able to void for the past 12 hours. He reports that prior to this presentation he has had several months of increased need to urinate at night, and he has been drinking a lot of fluids for "the flu." On physical examination his bladder is palpable between the pubis and the umbilicus, and he has an enlarged prostate gland without nodules.

This is acute urinary retention with underlying benign prostatic hypertrophy. Place an indwelling bladder catheter to be left for at least 3 days. Long-term management will be based on the use of alpha-blockers and 5-alpha-reductase inhibitors.

> On postoperative day 2 after inguinal hernia repair, a patient presents to the surgeon's office complaining that he "cannot hold his urine." Further questioning reveals that every few minutes he urinates a few drops of urine. On physical examination there is a large palpable mass arising from the pelvis and reaching almost to the umbilicus. The surgical wound is well healed, with no erythema or fluctuance.

This is a common presentation of acute urinary retention with overflow incontinence that can also occur immediately postoperatively in the recovery room, especially in patients whose surgery was performed utilizing spinal anesthesia. Manage with an indwelling bladder catheter.

> A 42-year-old woman complains to her primary care doctor that whenever she sneezes or laughs, she leaks a small amount of urine. Her past medical history is significant for hypothyroidism and 4 vaginal deliveries. She can tolerate the problem but inquires about surgical options.

This is a case of stress incontinence; the pelvic floor has been weakened by her vaginal deliveries. If she has no physical exam abnormalities, she should be taught exercises that strengthen the pelvic floor; if she has a large cystocele, she will need surgical reconstruction.

Stones

Passage of **ureteral stones** produces the classic colicky flank pain, with radiation to the inner thigh and labia or scrotum; it is sometimes associated with nausea and vomiting. Most stones are visible on noncontrast CT scan. Although there are a variety of endoscopic and other modalities to address retained urinary stones, intervention is not always needed.

- Small stones (≤3 mm) at the ureterovesical junction have a high likelihood of passing spontaneously and can be handled with analgesics, fluids, and watchful waiting.
- Large stones are less likely to pass spontaneously and require intervention. The most common tool used is extracorporeal shock wave lithotripsy (ESWL). Sometimes ESWL cannot be used (e.g., pregnant women, bleeding diathesis, stones that are several centimeters large). Other options include endoscopic basket extraction, laser, and open surgery.

Miscellaneous

Pneumaturia is almost always caused by fistulization between the bladder and the GI tract, most commonly the sigmoid colon, and most commonly from diverticulitis (second possibility is cancer of the sigmoid; cancer of the bladder is a very distant third). Men > women, as the uterus buffers the bladder from the GI tract. Workup starts with CT scan, which will show the inflammatory diverticular mass. Colonoscopy is needed later to rule out cancer. Surgical treatment is required.

Erectile dysfunction (ED), or impotence, is defined as an inability to get or maintain an erection. The etiology can be organic or psychogenic.

- **Psychogenic impotence** has sudden onset, is partner- or situation-specific, and usually does not interfere with nocturnal erections. Psycho- or behavioral therapy may be beneficial, or the condition may be self-limited.
- **Organic impotence** has a physiological etiology: most commonly nerve damage (trauma, pelvic surgery) or vascular (arteriosclerosis, diabetes). Neurological etiologies are acute (i.e., immediately following the event there is impotence), as opposed to vascular etiologies which tend to be gradual, progressing from erections not lasting long enough, to being of poor quality, to not happening at all.

Sildenafil, tadalafil, and vardenafil have become first choice treatment in many cases, but there are many options, such as prosthetic implants and vascular reconstruction, for traumatic arterial injury (rare).

> A 72-year-old man who in previous years passed 3 urinary stones is again having symptoms of ureteral colic. He has relatively mild pain that began 6 hours ago but has no real nausea or vomiting. CT shows a 3-mm ureteral stone just proximal to the ureterovesical junction.

Although many tools exist for the management of ureteral stones, small stones will ultimately pass on their own and do not require invasive procedures. Hydrate and manage pain.

> A 54-year-old woman has a severe ureteral colic. CT shows a 9-mm ureteral stone at the ureteropelvic junction.

Larger stone that the previous scenario, therefore less likely to pass spontaneously. The best option is lithotripsy, with endoscopic extraction the next best (more invasive).

> A 72-year-old man has for the past several days noticed bubbles of air coming out with the urine when he urinates. He has mild abdominal pain and a low-grade fever.

Pneumaturia is caused by a fistula between the bowel and the bladder, most commonly from sigmoid colon to dome of the bladder caused by diverticulitis. Cancer (also originating in the sigmoid) is the second possibility.

Intuitively you would think that cystoscopy or sigmoidoscopy would verify the diagnosis, but in reality these are low-yield, as are contrast studies (cystogram, barium enema). CT is the most sensitive diagnostic tool. Because ruling out cancer of the sigmoid is important, the sigmoidoscopic examination would be done at some point, but not as the first test. Eventually surgery will be needed.

> A 32-year-old man has sudden onset of impotence. One month ago he was unexpectedly unable to perform with his wife after an evening of heavy eating and heavier drinking. Ever since then he has not been able to achieve an erection when attempting to have intercourse with his wife, but he still gets nocturnal erections and can masturbate normally.

A classic case of psychogenic impotence: young man, sudden onset, partner-specific. Typically this is reversible with psychotherapy.

> A 66-year-old diabetic man with generalized arteriosclerotic occlusive disease notices gradual loss of erectile function. At first he could get erections, but they did not last long; later the quality of the erection was poor, and eventually he developed complete impotence. He does not get nocturnal erections.

This vignette describes the classic pattern of organic impotence not related to trauma. A wide range of therapeutic options exists, but probably the first choice now is sildenafil.

Pediatric Urology

A **posterior urethral valve** is the most common reason a newborn boy doesn't urinate during day 1 of life (also look for meatal stenosis). Gentle catheterization can be done to empty the bladder (the valves will not present an obstacle to the catheter). Voiding cystourethrogram is the diagnostic test, and endoscopic fulguration or resection is curative.

Hypospadias is easily noted on the neonatal physical exam. The urethral opening is on the ventral side of the penis, somewhere between the tip and the base of the shaft.

UTI in children should always lead to a urologic workup. The cause may be vesicoureteral reflux, or some other congenital anomaly. **Vesicoureteral reflux** and infection produce burning on urination, frequency, low abdominal and perineal pain, flank pain, and fever and chills in a child. Start treatment of the infection (empiric antibiotics first, followed by culture-guided choice), and do an IVP and voiding cystogram looking for the reflux. If found, use long-term antibiotics until the child "grows out of the problem."

Note

Circumcision should never be done on a child with hypospadias, as the skin of the prepuce will be needed for the plastic reconstruction that will eventually be done.

Low implantation of a ureter is usually asymptomatic in men but can be symptomatic in women: the patient feels normally the need to void and voids normally at appropriate intervals (urine deposited into the bladder by the normal ureter), but is also wet with urine all the time (urine that drips into the vagina from the low implanted ureter). If physical examination does not find the abnormal ureteral opening, IVP is diagnostic. Surgery is corrective.

Ureteropelvic junction obstruction allows normal urinary output without difficulty, but if a large diuresis occurs, the narrow area cannot handle it. The classic presentation is an adolescent who goes on a beer-drinking binge for the first time and develops colicky flank pain.

> You are called to the nursery to see an otherwise healthy-looking newborn because he has not urinated in the first 24 hours of life. Physical examination shows a big distended urinary bladder and a normal meatus.

Infants are not born alive if they have no kidneys (without kidneys, lungs do not develop), so this represents some form of obstruction. First look at the meatus: it could be simple meatal stenosis. If it is not, a posterior urethral valve is the most likely diagnosis. Drain the bladder with a catheter, perform a voiding cystourethrogram, and treat with endoscopic fulguration or resection.

> A 9-year-old boy presents with 3 days of burning on urination, increased frequency, low abdominal and perineal pain, left flank pain, and fever and chills.

Boys rarely get UTI. Treat the infection, of course, but do an IVP and voiding cystogram looking for reflux. If found, long-term antibiotics are indicated.

> A mother brings her 6-year-old girl to you because "she has failed miserably to get proper toilet training." On questioning you find out that the little girl perceives normally the sensation of having to void and voids normally and at appropriate intervals, but also happens to be wet with urine all the time.

A classic vignette: low implantation of one ureter. In boys there would be no symptoms because low implantation is still above the sphincter, but in girls the low ureter empties into the vagina and has no sphincter. The other ureter is normally implanted and accounts for her normal voiding pattern. If the vignette did not include physical exam, that would be the next step, which might show the abnormal ureteral opening. Often physical examination does not reveal the anomaly, and imaging with IVP is necessary. Surgery is curative.

> A 16-year-old boy goes on a beer-drinking binge at the end of the school year. Shortly thereafter he develops colicky flank pain.

Another classic vignette: ureteropelvic junction obstruction. Diagnose with U/S and correct surgically.

Oncology

Hematuria is the most common presentation for cancers of the kidney, ureter, or bladder. Most cases of hematuria are caused by benign disease, but any patient presenting with this condition should get a workup to rule out cancer. Workup should begin with CT and continue with cystoscopy, which is the only reliable way to rule out cancer of the bladder.

Renal cell carcinoma in its full-blown picture produces hematuria, flank pain, and a flank mass. It can also produce hypercalcemia, erythrocytosis, and elevated liver enzymes. That full-blown picture is rarely seen today, since most patients are worked up as soon as they have hematuria.

CT typically demonstrates a mass to be a heterogenic solid tumor and needs to be assessed for renal vein and IVC involvement. Surgery is curative, and may include partial nephrectomy, radical nephrectomy, and even en bloc inferior vena cava resection and reconstruction.

Cancer of the bladder (transitional cell cancer in most cases) has a very close correlation with smoking and usually presents with hematuria. Sometimes there are irritative voiding symptoms, and patients may have been treated for UTI in the past. Diagnosis is made by CT and followed by cystoscopy. Both surgery and intravesicular BCG have therapeutic roles, but a very high rate of local recurrence makes lifelong close follow-up a necessity.

Prostatic cancer incidence increases with age. Most are asymptomatic and are discovered by screening rectal exam (hard, nodular gland) or serum prostatic specific antigen (PSA). Transrectal needle biopsy establishes diagnosis. CT helps assess extent and type of therapy. Surgery and/or radiation are choices. Bone metastases occur, but typically respond to androgen ablation (medical utilizing luteinizing hormone-releasing hormone agonists or antiandrogens like flutamide or surgical via orchiectomy).

Testicular cancer affects young men, in whom it presents as a painless testicular mass.

- Because benign testicular tumors are virtually nonexistent, biopsy is not done, and a radical orchiectomy is performed by the inguinal route.
- Blood samples are taken pre-op for serum markers (α-fetoprotein [AFP] and β-human chorionic gonadotropin [β-HCG]), which will be useful for follow-up to identify recurrent disease if elevated initially.
- Most testicular cancer is exquisitely radiosensitive and chemosensitive (platinum-based chemotherapy), offering many options for successful treatment even in cases of clinically advanced, metastatic disease.

> A 70-year-old man presents to his primary care physician with hematuria. On exam he has tenderness over the left flank, and a mass is palpable.

This is most suspicious for renal cell carcinoma. Start the workup with a CT of the abdomen and pelvis with IV contrast.

> A 55-year-old smoker with hypertension and diabetes reports 3 instances of painless hematuria over the past 2 weeks. In the past 2 months he has been treated twice for UTI, although cultures were negative. He does not recall having fever.

Bladder cancer can be irritative, present with symptoms misdiagnosed as a UTI, and treated with antibiotics. In retrospect there is usually no fever, and cultures are negative as the culprit is cancer and not infection. Start with a CT to rule out a renal source; then proceed with cystoscopy.

Clinical Pearl

On the exam, beware of an answer choice with "transscrotal biopsy" to evaluate a testicular mass. It seems reasonable, but is absolutely contraindicated and thus a common exam distractor. Serum tumor markers are drawn preoperatively but do not impact the need for resection, i.e., orchiectomy is still indicated even if negative.

A 59-year-old black man is told by his primary care physician that his prostatic-specific antigen (PSA) has increased significantly since his last visit. He has no palpable abnormalities in his prostate by rectal exam.

In the current era of prostate cancer screening, this is the most common presentation. Start with a transrectal needle biopsy. Management is surgical prostatectomy or radiation, depending on the extent of disease and patient preference.

A 62-year-old man had a radical prostatectomy for cancer of the prostate 3 years ago. He presents today with low back pain. Bone scan shows metastases throughout the entire skeleton.

Prostate cancer, unfortunately, has a tendency to metastasize to bone. It can be quite painful initially. Treatment is as follows:

- Androgen ablation: short-term (1–2 years), but can provide dramatic palliation
- Medical ablation: luteinizing hormone-releasing hormone agonists and antiandrogens (flutamide) (**preferred method**)
- Surgical orchiectomy

A 25-year-old man presents with a painless, hard testicular mass.

There are no benign solid masses of the testicle. Physical exam must be certain to rule out epididymal origin, and if it feels cystic an U/S is indicated. Otherwise no imaging is necessary: proceed directly to radical orchiectomy by the inguinal route for both diagnosis and treatment. Serum tumor markers should be checked prior to surgery for long-term surveillance. Administer adjuvant platinum-based chemotherapy postoperatively.

A 25-year-old man is found on a pre-employment chest x-ray to have multiple bilateral pulmonary nodules. On physical examination a hard testicular mass is found. He reports several months of unintentional weight loss.

Similar presentation to the previous case, although now with metastatic disease. Despite this fact, testicular cancer is very chemosensitive, so the treatment is the same: platinum-based chemotherapy and surgical orchiectomy.

Orthopedics 4

Learning Objectives

- ❑ Understand the different types of fracture and their treatments
- ❑ Know the syndromes that affect various nerves and tendons
- ❑ Know the bone tumors seen in adults versus children

ADULT ORTHOPEDICS

X-rays for suspected fracture in adults should always include the following:

- Two views at 90° to one another
- Joints above and below the broken bone
- Bones that are in "the line of force" of the injury (e.g., lumbar spine following a vertical fall)

Generally, broken bones that are not badly displaced or angulated or that can be satisfactorily aligned by external manipulation can be immobilized in a cast ("**closed reduction**"). Broken bones that are severely displaced or angulated or that cannot be aligned easily require surgical intervention to reduce and fix the fracture ("**open reduction and internal fixation**").

Upper Extremities

Clavicular fracture typically occurs at the junction of middle and distal thirds. It is treated by placing the arm in a sling. The historical "figure-of-8" bandage is no longer used.

Humerus fracture is typically managed with casting. The **radial nerve** can be injured in oblique fractures of the middle to distal thirds of the humerus. If a patient is unable to dorsiflex (extend) the wrist but regains function when the fracture is reduced and the arm is placed on a hanging cast or coaptation sling, no surgical exploration is needed. However, if nerve paralysis develops or remains after reduction, the nerve is entrapped and surgical exploration is mandatory.

Anterior dislocation of the shoulder is the more common direction of shoulder dislocation. Patients hold the arm close to their body, but rotated outward as if they were going to shake hands. There may be numbness in a small area over the deltoid from stretching of the axillary nerve. Anteroposterior (AP) and lateral x-rays are diagnostic. Some patients develop recurrent dislocations with minimal trauma.

Posterior shoulder dislocation is rare and occurs after massive uncoordinated muscle contractions, such as an epileptic seizure or an electrical burn. The arm is held in the protective position: close to the body and internally rotated. Regular x-rays can easily miss it; axillary views or scapular lateral views are needed.

Colles fracture is a fairly common fracture of the distal radius and styloid process of the ulna that results from a fall on an outstretched hand, often in older patients with osteoporosis. The deformed and painful wrist looks like a "dinner fork." The main abnormality seen on x-ray is a dorsally displaced, dorsally angulated fracture of the distal radius. Treatment is with close reduction and long arm cast.

Monteggia fracture results from a direct blow to the ulna resulting in a diaphyseal fracture of the proximal ulna with anterior dislocation of the radial head. The classic scenario of a Monteggia fracture is a raised protective arm hit by police baton.

Galeazzi fracture is the mirror image: the distal third of the radius gets the direct blow and has the fracture, and there is dorsal dislocation of the distal radioulnar joint. In both, the broken bone requires open reduction and internal fixation, and the dislocated one is managed with closed reduction.

Fracture of the scaphoid (carpal navicular fracture) tends to occur in a young adult who falls on an outstretched hand. The chief complaint is typically wrist pain, with physical exam revealing localized tenderness to palpation over the anatomic snuff box. In nondisplaced fractures, x-rays are usually negative, but thumb spica cast is indicated just with the history and physical findings, as x-rays will not demonstrate the fracture for 2–3 weeks. If original x-ray shows displaced and angulated fracture, open reduction and internal fixation are needed.

Metacarpal neck fracture (typically the fourth or fifth, or both) happens when a closed fist hits a hard surface (like a wall). The hand is swollen and tender, and x-rays are diagnostic. Treatment depends on the degree of angulation, displacement, or rotary malalignment: closed reduction and ulnar gutter splint for the mild fractures vs. wire or plate fixation for markedly displaced fractures.

Carpal tunnel syndrome occurs following repetitive hand work such as typing and presents with numbness and tingling in both hands in the distribution of the median nerve (radial 3½ fingers). The symptoms can be reproduced by hanging the hand limply for a few minutes, or by tapping, percussing, or pressing the median nerve over the carpal tunnel (Tinel sign). The diagnosis is clinical, but x-rays should be performed to rule out other pathology. Initial treatment is splinting and anti-inflammatory agents. If these conservative measures fail, perform electromyography and nerve conduction velocity testing and surgically release.

Stenosing tenosynovitis ("**trigger finger**") is more common in women than men and presents with acute finger flexion and the inability to extend it unless pulled with the other hand, which results in a painful "snap." Steroid injection is the first line of treatment; surgery is the treatment of last resort.

De Quervain tenosynovitis is more common in women than men and is often seen after pregnancy. Repetitive activities with the thumb in extension and abduction (pinching, grasping) result in irritation and inflammation of the thumb extensor tendons. Patients complain of pain along the radial side of the wrist and the first dorsal compartment. On physical exam the pain can be reproduced by asking her to hold the thumb inside her closed fist, then forcing the wrist into ulnar deviation. Splint and anti-inflammatory agents can help, but steroid injection is most effective. Surgery is rarely needed.

Clinical Pearl

Scaphoid fracture is notorious for a very high rate of nonunion, secondary to avascular necrosis.

Dupuytren contracture occurs in older men of Norwegian ancestry and in alcoholics. There is contracture of the palm of the hand, and palmar fascial nodules can be felt. Urgent surgery may be necessary but is usually not required.

A **felon** is an abscess in the pulp of a fingertip, often secondary to a neglected penetrating injury. Patients complain of throbbing pain and have all the classic findings of an abscess, including fever. Because the pulp is a closed space with multiple fascial trabecula, pressure can build up and lead to tissue necrosis; urgent surgical drainage is necessary. **Do not confuse this with a paronychial infection**.

Gamekeeper's thumb (or skier's thumb) is an injury of the ulnar collateral ligament sustained by forced hyperextension of the thumb. On physical exam there is collateral laxity at the thumb-metacarpophalangeal joint. If untreated, it can be dysfunctional and painful and lead to arthritis. Manage with casting.

Jersey finger is an avulsion injury to the flexor digitorum profundus tendon sustained when the flexed finger is forcefully extended (as in someone unsuccessfully grabbing a running person by the jersey). When making a fist, the distal phalanx of the injured finger does not flex with the others.

Mallet finger is the opposite: the extended finger is forcefully flexed (a common volleyball injury), and the extensor tendon is ruptured. The tip of the affected finger remains flexed when the hand is extended, resembling a mallet. For both injuries, **splinting** is the first line of treatment.

Traumatically amputated digits are surgically reattached whenever possible. The amputated digit should be cleaned with sterile saline, wrapped in a saline-moistened gauze, placed in a sealed plastic bag, and the bag placed on a bed of ice. The digit should not be placed in antiseptic solutions or alcohol, should not be put on dry ice, and should not be allowed to freeze.

> A 55-year-old woman falls in the shower and injures her right shoulder. She presents to the ED with her arm held close to her body and rotated outward. She is in pain and will not move the arm from that position. There is numbness in a small area of her shoulder over the deltoid muscle.

This is a typical description of an anterior dislocation of the shoulder with axillary nerve damage. Diagnose with AP and lateral x-rays and reduce.

> A 22-year-old woman with epilepsy presents to the ED following a grand mal seizure. She has recovered her mental status and complains of pain in her right shoulder, which she cannot move. AP and lateral x-rays do not demonstrate any abnormality.

Despite the normal x-ray, this is a common presentation of a posterior dislocation of the shoulder. Perform axillary view or scapular lateral view x-rays to confirm and then reduce.

Clinical Pearl

Historically, gamekeeper's thumb was suffered by gamekeepers when they killed rabbits by dislocating their necks with an extended thumb. On the exam, this is more likely to present as a skiing-related injury, as the thumb gets stuck in the ski strap during a fall.

A 19-year-old woman falls on an outstretched hand and presents to the ED complaining of wrist pain. On physical examination there is tenderness to palpation over the snuff box; AP and lateral x-rays demonstrate no abnormality.

Another classic scenario, this is a fracture of the scaphoid bone (carpal navicular). These are notorious because x-rays will not show them for 2–3 weeks, and they have a high rate of non-union due to avascular necrosis. The history and physical findings are sufficient to justify the use of a thumb spica cast, with repeat x-rays 2–3 weeks later.

A 19-year-old woman falls on an outstretched hand and presents to the ED complaining of wrist pain. On physical examination there is tenderness to palpation over the snuff box; AP and lateral x-rays demonstrate displaced scaphoid fracture.

Displaced and angulated scaphoid fractures require open reduction and internal fixation.

During a barroom fight, a 22-year-old man punches a bystander and ends up in the ED with a swollen and tender right hand. X-ray shows fractures of the fourth and fifth metacarpal necks.

A common cause of this fracture pattern. Treatment depends on the degree of angulation, displacement, and malalignment: closed reduction and splint for mild fractures, wire/plate fixation for more severe fractures.

A 48-year-old man breaks his arm when he falls down the stairs. X-rays demonstrate an oblique fracture of the middle to distal thirds of the humerus. Physical examination shows that he cannot dorsiflex his wrist.

Fractures of the humeral shaft can injure the radial nerve, which courses in a spiral groove right around the posterior aspect of that bone. However, surgical exploration is not usually needed. A hanging arm cast or coaptation splint are used, and the nerve function returns eventually. However, if the nerve was okay when the patient came in and becomes paralyzed after closed reduction of the bone, the nerve has been trapped; surgical exploration is necessary.

A 33-year-old carpenter accidentally drives a small nail into his index finger, but it stops bleeding and he applies a bandage. Two days later he shows up in the ER with throbbing pain, fever, and redness.

This kind of abscess is called a felon, and like all abscesses it must be drained. This should be done urgently, as it is a tight space and delay can lead to compartment syndrome and necrosis. **Do not confuse this with a paronychial infection**.

As a young man falls while skiing, he jams his thumb into the snow. Physical examination shows collateral laxity at the thumb metacarpophalangeal joint.

Historically called "gamekeeper's thumb," this is an injury to the ulnar collateral ligament of the thumb. It should be casted; otherwise dysfunctional joint and long-term arthritis may occur.

Emergency medical services arrives at the scene of a factory accident where a 32-year-old man has severed his right index finger.

Clean the digit with sterile saline, wrap it in saline-moistened gauze, and place it in a plastic bag on a bed of ice. Transport to the nearest center that performs reimplantation.

Lower Extremities

Hip fracture is a misnomer for fractures that involve the proximal femur. These fractures typically occur in the elderly following a fall; the hip hurts and the patient's position in the stretcher is one in which the affected leg is shortened and externally rotated. Treatment depends on precise location.

Femoral neck fracture, particularly if displaced, compromises the tenuous blood supply of the femoral head. To achieve faster healing and earlier mobilization, replace the femoral head with a prosthesis.

Intertrochanteric fracture is less likely to lead to avascular necrosis and is usually treated with open reduction and pinning. The unavoidable immobilization increases risk for DVT/PE, mandating chemical and mechanical prophylaxis.

Femoral shaft fracture (common) often requires operative management in adults with intramedullary rod fixation.

- If bilateral or comminuted, may result in significant blood loss and hemodynamic instability; external fixation may control some degree of hemorrhage
- If open, it is an orthopedic emergency requiring irrigation and closure in the OR within 6 hours

Posterior dislocation of the hip occurs when the femur is driven backward, such as in a head-on car crash where the knees hit the dashboard. The patient has hip pain and lies in the stretcher with the leg shortened, adducted, and internally rotated. Because of the tenuous blood supply of the femoral head, emergency reduction is needed to avoid avascular necrosis.

Knee injury typically produces swelling of the knee; any knee pain without swelling is unlikely to be a serious knee injury. Collateral ligament injury is usually sustained when the force of impact is at the side of the knee, a common sports injury. Medial forces to the knee generally result in disruption of the lateral ligament, and vice versa.

- The knee will be swollen, and there is localized pain by direct palpation on the affected side.
- With the knee flexed 30°, passive abduction or adduction will produce pain on the torn ligaments and allow further displacement than the normal leg.

Clinical Pearl

With femoral fracture, be alert for fat embolism leading to severe respiratory distress, which typically requires mechanical ventilation. This is rare occurrence, but is a concept often seen on the exam.

Clinical Pearl

The leg is also shortened due to a hip fracture, but then it tends to be externally rotated, as opposed to in a posterior dislocation where it is internally rotated.

- Abduction demonstrates the medial injuries (valgus stress test), whereas adduction diagnoses the lateral injuries (varus stress test).
- Diagnosis is made with MRI.
- Isolated injuries are treated with a hinged cast.
- When several ligaments are torn, surgical repair is preferred.

Anterior cruciate ligament (ACL) injury is more common than posterior injury.

- There is severe knee swelling and pain.
- With the knee flexed 90°, the lower leg can be pulled anteriorly, like a drawer being opened ("anterior drawer test").
- A similar finding can be elicited with the knee flexed at 20° by grasping the thigh with one hand and pulling the leg with the other (Lachman test).

Posterior cruciate ligament (PCL) injury produces the opposite findings on physical exam. MRI is diagnostic. Sedentary patients may be treated with immobilization and rehabilitation, whereas athletes require arthroscopic reconstruction.

Clinical Pearl

Injuries to the medial meniscus, medial collateral, and anterior cruciate often occur simultaneously.

Meniscal tear is difficult to diagnose clinically and on x-rays but is clearly demonstrated on MRI.

- Protracted pain and swelling after a knee injury with tenderness on exam
- Possible "catching and locking," which limits knee motion, and a "click" when the knee is forcefully extended
- Treatment is arthroscopic repair with attempt to preserve as much meniscus as possible; complete meniscectomy leads to the late development of degenerative arthritis

Posterior dislocation of the knee can result in an injury to the popliteal artery. Following reduction of the dislocation, the popliteal artery must be evaluated with U/S. If distal pulses were absent and returned following reduction, U/S may identify an intimal flap or local dissection. This would mandate further evaluation with CT angiogram. If pulses remain absent or U/S demonstrates a significant injury, surgical exploration is indicated. Delayed restoration of flow may require a prophylactic fasciotomy.

Tibial stress fractures ("shin splints") are most commonly seen in athletes and military trainees. There is tenderness to palpation over a very specific point on the bone, but x-ray is initially normal. Treat with a cast or non-weight bearing on crutches, and repeat the x-ray in 2 weeks.

Clinical Pearl

Because of the superficial location of the tibia, many fractures are open. These require surgical exploration for debridement, irrigation, and internal fixation.

Leg fracture involving the tibia and fibula is often seen when a pedestrian is hit by a car. Physical exam shows angulation; x-rays are diagnostic. Treatment is casting for fracture that is easily reduced and intramedullary nailing for fracture that is not easily reduced.

Compartment syndrome is an emergency that may be missed in the absence of a high index of suspicion. It occurs most frequently in the forearm or lower leg.

- Precipitating events include prolonged ischemia followed by reperfusion, crushing injuries, or other types of trauma; in the lower leg, by far the most common cause is a tibia/fibula fracture with closed reduction.
- The patient has pain and limited use of the extremity; palpation of soft tissue within the compartment feels very tight and tender to palpation. The most reliable physical finding is pain with passive extension.

- Pulses may be normal because tissue ischemia will result if compartment pressure exceeds the capillary perfusion pressure (~20–25 mm Hg), but distal pulses will remain until compartment pressure is greater than the mean arterial pressure (typically 50–60 mm Hg).
- Emergency fasciotomy is required for treatment.

Rupture of the Achilles tendon is often seen in middle-aged recreational athletes who subject themselves to severe strain (e.g., tennis). As they plant the foot and change direction, a loud popping noise is heard (like a rifle shot), and they fall clutching the ankle. Limited plantarflexion is still possible, but pain, swelling, and limping bring them to seek medical attention. Palpation of the tendon reveals a gap. Historically these injuries were treated with casting in equinus position; surgical repair is now the treatment of choice.

Fracture of the ankle occurs when falling on an inverted or everted foot. In either case, both malleoli break. AP, lateral, and mortise (angled) x-rays are diagnostic. If the fragments are displaced, open reduction and internal fixation are indicated.

Plantar fasciitis is a very common but poorly understood problem presenting with disabling, sharp pain on the sole of the foot or heel every time the foot contacts the ground. It tends to be worse in the morning. Physical exam is significant for exquisite tenderness to palpation, and X-ray may demonstrate a bone spur (although this may be incidental, as many patients have asymptomatic bone spurs). Management is symptomatic relief with eventual self-resolution.

Morton neuroma is an inflammation of the common digital nerve at the third interspace, between toes 3 and 4. The neuroma is palpable and exquisitely tender to palpation. The cause is typically the use of pointed, high heel shoes (or pointed cowboy boots) that force the toes to be bunched together. Management includes analgesics and more sensible shoes, but surgical excision can be performed if conservative management fails.

Gout typically produces swelling, redness, and exquisite pain of sudden onset at the first metatarsophalangeal joint in middle-aged obese men with high serum uric acid. Uric acid crystals are identified in fluid from the joint. Treatment for the acute attack is indomethacin and colchicine; treatment for chronic control is allopurinol and probenecid.

> A 77-year-old man falls in the nursing home and hurts his hip. He presents with the affected leg shortened and externally rotated. X-ray demonstrates a displaced femoral neck fracture.

The blood supply to the femoral head is compromised with femoral neck fractures; the patient is better off with a metal prosthesis rather than pinning the fracture.

> A 77-year-old man falls in the nursing home and hurts his hip. He presents with the affected leg shortened and externally rotated. X-ray demonstrates an intertrochanteric fracture.

There is less concern for avascular necrosis, and therefore these are repaired by open reduction and pinning. This is a prime setting for DVT, so the exam question may be geared toward prophylaxis.

Clinical Pearl

Falls from a significant height landing on the feet may have obvious leg or ankle fractures, but fractures of the lumbar or thoracic spine may be less obvious and must be assessed.

> An unrestrained woman in the front seat of a car crashes and sustains closed comminuted fractures of both femoral shafts. Shortly after presentation to the ED, she develops blood pressure 80/50 mm Hg and pulse 120/min. Abdominal and chest exam are normal. Focused abdominal sonography for trauma (FAST), chest x-ray, and pelvic x-ray are normal.

This is a throwback to the trauma vignettes to remind you that femur fractures can bleed significantly, and even cause hypovolemic shock. A full trauma evaluation is necessary to rule out other sources of bleeding, but manage these with external fixation and blood and fluid resuscitation until stable enough for definitive open reduction and internal fixation.

> An unrestrained woman in the front seat of a car crashes and sustains closed comminuted fractures of both femoral shafts. The fractures are externally fixated, and she is resuscitated. After remaining hemodynamically stable, she is transferred to the surgical ICU with plans for open fixation in the morning. Four hours after admission, she develops dyspnea, disorientation, and fever. Oxygen saturation is 84% on 4 L via nasal cannula.

Femoral fractures can lead to fat embolism presenting as respiratory distress or as severe as hypoxemic respiratory failure. Although rare, this is often tested. Support with supplemental oxygen and mechanical ventilation if necessary.

> The unrestrained front seat passenger in a car that crashes presents with pain in the right hip. He is hemodynamically stable and neurologically intact. On exam he is found to have a shortened right lower extremity that is adducted and internally rotated.

This is an orthopedic emergency: posterior dislocation of the hip. The blood supply of the femoral head is tenuous, and delay in reduction could lead to avascular necrosis. Confirm with x-ray and urgently reduce once other traumatic injuries have been ruled out.

> A college student tackled from the right side while playing football develops severe right knee pain. When examined shortly thereafter the knee is swollen, and he has pain on direct palpation over the medial aspect of the knee.

This is most likely an injury to the medial collateral ligament. Physical examination findings will likely include pain with passive abduction and an inability to abduct as far as the contralateral leg. MRI is diagnostic. A hinged cast is typically enough, but if multiple ligaments are injured surgical repair may be required.

A college student tackled while playing football develops severe knee swelling and pain. On physical examination with the knee flexed at 90°, the leg can be pulled anteriorly.

This is more likely an injury to the anterior cruciate ligament, with physical exam describing a positive anterior drawer test. Confirm with MRI. Sedentary patients may be treated just with immobilization and rehabilitation, but this patient is young and athletic and will require surgical repair.

A 19-year-old Army private presents to the base physician complaining of localized pain in his anterior leg. He is tender to palpation over the mid-tibia. X-ray is normal.

This is likely a tibial stress fracture, common in athletes and soldiers from overuse. They are not apparent on x-ray for up to several weeks. Presume there is a fracture and either cast or prescribe non-weight bearing with crutches for 2 weeks; then repeat the x-ray.

A pedestrian is hit by a car. Physical examination shows the leg to be angulated midway between the knee and the ankle. X-ray confirms fractures to the shaft of the tibia and fibula.

Leg fractures that are closed and can be easily reduced are managed with a cast; those that are open or cannot be aligned need open reduction and internal fixation, typically with an intramedullary nail.

A pedestrian is hit by a car. Physical examination shows the leg to be angulated midway between the knee and the ankle. X-rays confirm fractures of the shaft of the tibia and fibula. Satisfactory alignment is achieved, and a leg cast applied. In the ensuing 8 hours, the patient complains of increasing pain. When the cast is removed, the pain persists, the muscle compartments feel tight, and there is significant pain with passive extension of the toes. A dorsalis pedis pulse is palpable.

Compartment syndrome is a distinct hazard after fractures of the leg (and forearm). Urgent fasciotomy is indicated, as the symptoms did not improve with cast removal alone. Note that the presence of a pedis pulse does not rule out compartment syndrome.

A 49-year-old surgeon is playing a vigorous game of tennis when a loud "pop" is heard and he falls to the ground clutching his ankle. He limps off the courts, with pain and swelling in the back of the lower leg. He is still able to dorsiflex his foot.

This is a classic presentation for rupture of the Achilles tendon. Open surgical repair is the fastest option, although reasonable healing will eventually occur if casted in equinus position.

While running to catch a bus, an old man twists his ankle and falls on his inverted foot. X-rays demonstrate displaced fractures of both malleoli.

A very common injury. When the foot is forcefully rotated (in either direction), the talus pushes and breaks one malleolus and pulls off the other one. Open reduction and internal fixation are needed in this case because the fragments are displaced.

A window cleaner falls from a third story scaffold and lands on his feet. Physical examination and x-ray show comminuted fractures of both calcanei.

Obviously, the ankle fractures must be managed, but don't forget to evaluate for associated injuries based on the mechanism: compression fractures of the thoracic or lumbar spine. Start with x-ray. MRI may be necessary.

A 55-year-old obese man with diabetes and hypertension develops acute swelling, redness, and exquisite pain at the first metatarsophalangeal joints. He reports no history of trauma.

This presentation is consistent with an acute attack of gout. The joint is aspirated, and fluid analysis will demonstrate uric acid crystals. Treatment of the acute attack is indomethacin and colchicine. Long-term control of serum uric acid is done with allopurinol or probenecid.

Back

Clinical Pearl

If the "lightning" exits the foot by the big toe, it is L4–L5; if exits by the little toe, it is L5–S1.

Lumbar disk herniation occurs most commonly around age 45 at L4–L5 or L5–S1.

- Symptoms include several months of vague aching pain ("discogenic pain" produced by pressure on the anterior spinal ligament) before a sudden onset of "neurogenic pain" precipitated by a forced movement (patients cannot ambulate and they hold the affected leg flexed).
  - Neurogenic pain is often severe and characterized as "an electrical shock shooting down the leg"; it is exacerbated by coughing, sneezing, or defecating.
  - If the pain is not exacerbated by these activities, the problem is not a herniated disk.
- Straight leg-raising test reproduces excruciating pain and MRI confirms the diagnosis.
- Treatment for most patients is bed rest, physical therapy, and pain control, often enhanced by a regional nerve block. Surgical intervention is needed if neurologic deficits are progressing; emergency intervention is needed in the presence of cauda equina syndrome (distended bladder, flaccid rectal sphincter, or perineal saddle anesthesia).

Clinical Pearl

Many patients with ankylosing spondylitis have the HLA B-27 antigen, which is associated with other autoimmune disorders including inflammatory bowel disease and uveitis.

Ankylosing spondylitis is seen in men in decades 3–4 of life and presents with chronic back pain and morning stiffness. The pain is worse at rest and improves with activity. Symptoms are progressive, and x-rays reveal a "bamboo spine." Anti-inflammatory agents and physical therapy are effective.

Metastatic malignancy should be suspected in patients who have progressive back pain that is worse at night and unrelieved by rest or positional changes. It is often associated with weight

loss. The most common pathology is breast cancer metastases in women (lytic lesions) and prostate metastases in men (blastic lesions). Most are identifiable on x-ray, but CT and MRI are more sensitive. Pathological fractures are managed like any nonmalignant fractures.

> A 46-year-old man has sudden onset of severe back pain as he tries to lift a heavy object. The pain is like an electrical shock that shoots down his leg, and it prevents him from ambulating. On physical exam a straight leg-raise causes excruciating pain, and a flaccid rectal sphincter is noted.

Although likely caused by an acutely herniated disc, the presence of cauda equina syndrome is a surgical emergency.

> A 42-year-old man presents for further evaluation of back pain. He reports it has been present for 5–6 years but is intermittent. It manifests as morning stiffness and is worse at rest, but improves with activity. Two years ago he was treated for uveitis.

Think ankylosing spondylitis with progressive back pain and signs of autoimmune disorders. X-ray will eventually show "bamboo spine." Treatment is anti-inflammatory agents and physical therapy.

> A 72-year-old man presents with low back pain that is worse at night and not relieved by positional changes or over-the-counter analgesics. He is noted to have a 20-pound weight loss since his last visit, with no change in appetite.

Although back pain is common and often benign, weight loss is a red flag for possible malignancy. In this demographic, metastatic prostate cancer is a serious consideration. Include a prostate exam in your physical examination, and perform an x-ray and then likely an MRI.

Oncology

Most malignant bone tumors in adults are metastatic, from breast cancer in women (lytic lesions) and from prostate cancer in men (blastic lesions). Localized pain is an early finding. X-rays can be diagnostic, CT scans give more information, and MRI is even more sensitive. Lytic lesions commonly present as pathologic fractures.

Multiple myeloma is seen in older men and presents with fatigue, anemia, and localized pain at specific places on several bones. X-rays are diagnostic, showing multiple, "punched-out" lytic lesions. Urine protein electrophoresis (UPEP) demonstrates Bence-Jones protein, and abnormal immunoglobulins are seen in the blood on serum protein electrophoresis (SPEP). Treatment is chemotherapy.

Soft tissue sarcoma has relentless growth of soft tissue mass over several months. It is firm and typically fixed to surrounding structures. They can metastasize hematogenously to the lungs but do not invade the lymphatic system. MRI delineates the extent of the mass and degree of local invasion. Incisional biopsy to obtain tissue is diagnostic. Treatment includes wide local excision, radiation, and chemotherapy. Vascular reconstruction should be considered to enable limb-salvage surgeries.

Clinical Pearl

- In women, bone metastases are commonly due to lytic bone lesions from breast cancer (first) and lung cancer (second).
- In men, the most common etiology is prostate cancer, but metastatic lung cancer lesions more commonly result in pathological fractures.

Clinical Pearl

For metastatic malignancy, consider systemic treatment with chemotherapy, hormone therapy, or immunotherapy. Bone lesions have a better response compared with other sites of metastatic cancer.

> A 66-year-old woman picks up a bag of groceries and hears a snap. She presents to the ED in severe pain and is found to have a humerus fracture.

A pathologic fracture (i.e., for trivial reasons) is highly concerning for metastatic cancer. In older women, as in this case, this is most likely metastatic breast or lung cancer. Manage the fracture and workup for a primary cancer.

> A 60-year-old man complains of fatigue and pain at specific places on several bones. He is found to be anemic. X-ray shows multiple punched out lytic lesions throughout the skeleton.

Multiple lytic lesions in an older anemic man suggest multiple myeloma. X-rays are diagnostic, and additional tests include UPEP and SPEP. Treatment is chemotherapy.

> A 58-year-old woman has a soft tissue tumor in her thigh. It has been growing steadily for 6 months. It is located deep into the thigh, is firm and fixed to surrounding structures, and measures 8 cm in diameter.

Soft tissue sarcoma is the concern. Start with MRI to assess extent and neurovascular involvement, followed by incisional biopsy for tissue diagnosis. Management is multimodal consisting of surgery, radiation, and chemotherapy.

PEDIATRIC ORTHOPEDICS

Congenital dysplasia of the hip is familial and ideally should be diagnosed right after birth.

- Physical examination of the hips reveals uneven gluteal folds, and hips that can be easily dislocated posteriorly with a jerk and a "click" and returned to normal with a "snapping."
- If signs are equivocal, U/S is diagnostic. X-ray is not helpful, as the hip is not calcified in the newborn.
- Treatment is abduction splinting with a Pavlik harness for ~6 months.

Legg-Calve-Perthes disease is avascular necrosis of the capital femoral epiphysis and occurs around age 6, with insidious development of limping, decreased hip motion, and hip or knee pain.

- Patients walk with guarded passive motion of the hip and an antalgic gait (i.e., a gait that minimizes pain symptoms, from *anti-*, meaning "against," and *algo-*, meaning "pain").
- Diagnosis is confirmed with AP and lateral hip x-ray.
- Treatment is controversial, usually containing the femoral head within the acetabulum by casting and crutches.

Slipped capital femoral epiphysis (SCFE) (most common hip disorder in adolescents) is an orthopedic emergency because further slippage may compromise the blood supply and result in avascular necrosis of the femoral head. Patients are commonly overweight boys around age 13 who complain of groin or knee pain and ambulate with a limp.

- On physical exam there is limited hip motion, and as the hip is flexed the thigh goes into external rotation and cannot be rotated internally.
- Diagnostic testing is with x-ray.
- Treatment is surgical, e.g., pins to hold the femoral head back in place.

Septic hip (orthopedic emergency) is seen in toddlers who have had a febrile illness and then refuse to move the hip, i.e., they hold in flexed position with slight abduction and external rotation and experience pain with passive movement of the joint such as a diaper change.

- WBC count and erythrocyte sedimentation rate are elevated.
- Diagnosis is made by aspiration of the hip under general anesthesia, and surgical irrigation and open drainage are performed if pus is obtained.

Acute hematogenous osteomyelitis occurs in children who have had a febrile illness and presents as severe localized pain in a bone with no history of trauma.

- Diagnosis is with MRI, as x-ray will not be revealing for several weeks.
- Treatment is IV antibiotics.

Genu varum (bow-legs) is normal up to age 3; no treatment is needed. Persistent varus >3 years old is most commonly Blount disease, a disturbance of the medial proximal tibial growth plate for which surgery is corrective. **Genu valgus (knock-knee)** is normal age 4–8; no treatment is needed.

Osgood-Schlatter disease (osteochondrosis of the tibial tubercle) is seen in teenagers with persistent pain right over the tibial tubercle, which is aggravated by contraction of the quadriceps.

- Physical exam shows localized pain right over the tibial tubercle in the absence of knee swelling.
- Treatment is rest, ice, compression, and elevation. If there is no response, immobilize the knee in an extension or cylinder cast for 4–6 weeks.

Clubfoot (talipes equinovarus) presents at birth: both feet are turned inward and there is plantar flexion of the ankle, inversion of the foot, adduction of the forefoot, and internal rotation of the tibia. Serial plaster casts started in the neonatal period provide sequential correction starting with the adducted forefoot, then the hindfoot varus, and last the equinus. About 50% of patients with clubfoot are fully corrected this way. The other 50% require surgery after age 6–8 months, but before age 1–2 years.

Scoliosis is seen in adolescents and occurs when the thoracic spine is curved >10° to the right or left. The deformity progresses until skeletal maturity is reached (at the onset of menses, skeletal maturity is ~80%). In addition to the cosmetic deformity, severe cases develop decreased pulmonary function.

- Diagnosis is with physical exam from behind, with the patient bending forward.
- Treatment is bracing, which can arrest progression and surgery for severe cases.

> In the newborn nursery of a hospital, a child is noted to have uneven gluteal folds. Physical examination reveals that the right hip can be palpably dislocated posteriorly.

This is a straightforward description of developmental dysplasia of the hip (congenital dislocation of the hip). Physical examination should suffice, but if there is any doubt do an U/S. Treatment is abduction splinting using a Pavlik harness.

> A 6-year-old boy has progressive limping with decreased hip motion. He complains occasionally of knee pain on that side. Passive motion of the hip is guarded.

In this age group, the most likely diagnosis is Legg-Calve-Perthes disease (avascular necrosis of the capital femoral epiphysis). Remember that hip pathology can show up with knee pain. Diagnose with AP and lateral x-ray. Management is containment of the femoral head within the acetabulum by casting and crutches.

> A 13-year-old obese boy complains of pain in the thigh and knee and his mother reports progressive limping. Physical examination is normal for the knee but shows limited hip motion. As the hip is flexed, the leg rotates externally and cannot be rotated internally.

Although the physical exam findings are classic, the age group and chief complaint are enough to make the most likely diagnosis slipped capital femoral epiphysis, an orthopedic emergency. Confirm with anteroposterior and lateral x-rays, and manage surgically with femoral head fixation.

> A 3-year-old boy demonstrates limited mobility. His mother carries him into the ED and reports the symptoms started a few days after he had a "cold" that was going around the house. He appears to be in pain and holds the leg with the hip flexed, in slight abduction and external rotation. You cannot examine that hip with eliciting pain.

This presentation is very concerning for a septic hip, another orthopedic emergency. Check bloodwork, including a CBC and ESR, and aspirate the hip to confirm the diagnosis. Treatment is drainage via open arthrotomy.

> An 8-year-old boy is brought to the pediatrician due to unrelenting mid-tibial pain. His mother reports no trauma, but he did have a "cold" that went around the house the previous week, including high fever.

The "cold" was likely a bacterial infection that has now seeded the bone and caused acute hematogenous osteomyelitis. MRI is diagnostic (x-ray will not be revealing for several weeks). Administer IV antibiotics.

A 14-year-old boy says he injured his knee while playing football. Although there is no swelling of the knee joint, he complains of persistent pain right over the tibial tubercle, which is acutely tender to palpation.

Osteochondrosis of the tibial tubercle (Osgood-Schlatter disease) is often mistaken for a sports-related injury, but there is no joint swelling and the tenderness is focal at the tibial tuberosity. Treatment is conservative: rest, ice, compression, and mobilization. If symptoms progress, immobilize the knee in a cast for 4–6 weeks.

Fracture

Pediatric fractures are different from adult fractures in 2 ways:

- The rate of healing is much faster in children.
- Remodeling occurs to a greater degree in children, allowing for tolerance of angulation that would be acceptable in adults.

There are 2 exceptions to note: supracondylar fractures of the humerus and fractures of any bones that involve the growth plate or epiphysis.

- Supracondylar fractures of the humerus (after hyperextension of the elbow in a child who falls on the hand with arm extended)
  - These injuries are particularly dangerous due to the proximity of the brachial artery and ulnar nerve.
  - Although treatment is standard casting or traction, it requires careful monitoring of vascular and nerve integrity and vigilance regarding the development of compartment syndrome.
- Fractures that involve the growth plate or epiphysis
  - Salter-Harris (SH) classification is used to grade epiphyseal fractures; SH I and II fractures can often be managed without surgery, but ≥III typically require operative management.
  - Treatment is closed reduction if the fracture does not cross the growth plate or involve the joint.
  - Treatment is open reduction and internal fixation if the growth plate is fractured into 2 pieces; this will ensure precise alignment and even growth to avoid chronic deformity of the extremity.

A 4-year-old boy falls down the stairs and fractures his humerus. He is placed in a cast at the nearby urgent care center and seen by his regular pediatrician 2 days later. He does not appear to be in pain; however, the x-ray demonstrates significant angulation of the broken bone.

No intervention is indicated. Except for rotational deformities, children have such tremendous ability to heal and remodel broken bones that almost any reasonable alignment and immobilization will end up with a good result.

An 8-year-old boy falls on his right hand with the arm extended and presents to the ED in significant pain. X-ray reveals a supracondylar fracture of the humerus. The distal fragment is displaced posteriorly.

This type of fracture is common in children, but it is significant because it may produce vascular or nerve injury (or both) and thus result in a Volkmann contracture. Although it can usually be treated with appropriate casting or traction, a careful vascular and neurological exam is mandatory to rule out traumatic injury, as well as to assess continuously for compartment syndrome.

Pediatric Orthopedic Oncology

Primary malignant bone tumors are diseases of young people. They present with persistent low-grade pain for several months.

Osteogenic sarcoma (most common primary malignant bone tumor):

- Seen age 10–25, usually around the knee (lower femur or upper tibia)
- Typical "sunburst" pattern often described on x-ray

Ewing sarcoma (second most common malignant bone tumor):

- Seen in younger children (age 5–15)
- Grows in the diaphyses of long bones
- Typical "onion skinning" pattern often described on x-ray

A 16-year-old boy complains of low-grade but constant pain in the distal femur present for several months. He has local tenderness in the area but is otherwise asymptomatic. X-ray shows a large bone tumor breaking through the cortex into the adjacent soft tissues and exhibiting a "sunburst" pattern.

A 10-year-old complains of persistent pain deep in the middle of the thigh. X-ray shows a large, fusiform bone tumor pushing the cortex out and producing periosteal "onion skinning."

Primary malignant bone tumors are also diseases of young people. The extent of the exam is diagnosis and recognition of the x-ray patterns of each; management is highly specialized and unlikely to be tested.

Cardiovascular Surgery 5

Learning Objectives

- ❑ Recognize presentation, diagnosis, and management of pediatric and adult heart problems
- ❑ Describe surgical issues related to diseases of the lung
- ❑ Recognize the common etiologies of mediastinal masses
- ❑ Comprehend the common procedures in vascular surgery, including indications, complications, and alternatives

CONGENITAL HEART DISEASE

Vascular ring is an aberrant formation of the aorta and great vessels that creates extrinsic compression of the trachea and/or esophagus.

- Initial symptoms include stridor and episodes of respiratory distress with "crowing" respiration, during which the baby assumes a position with an extended neck (relieves the compression).
- Later symptoms revolve around difficulty with feeding or swallowing.
- If only the respiratory symptoms are present, consider tracheomalacia.

Barium swallow demonstrates extrinsic compression from the abnormal vessel. Bronchoscopy shows segmental tracheal compression and rules out diffuse tracheomalacia. CT or MRI will help to reveal details of the vascular anatomy and help plan for surgical repair. Surgery divides the smaller of the two aortic arches.

Cardiac anomalies (congenital or acquired) are best diagnosed with an echocardiogram.

Left-to-right shunts share the presence of a loud, holosystolic (pansystolic) murmur and overloading of the pulmonary circulation, with resultant long-term damage to the pulmonary vasculature. The volume and consequences of the shunt vary depending upon their location.

- **Atrial septal defect** (ASD) has a very minor, low-pressure, low-volume shunt. Patients typically grow into late infancy before it is recognized. A faint pulmonary flow systolic murmur and fixed split second heart sound are characteristic. A history of frequent colds is elicited. Echocardiogram is diagnostic. Treatment is surgical or percutaneous closure.

- **Ventricular septal defect** (VSD) can range from minor to significant:
  - Small, restrictive defects low in the muscular septum have minimal pathophysiological effect and typically close spontaneously by age 3.
  - Defects high in the membranous septum (more common) can be more problematic, resulting in "failure to thrive," a loud pansystolic murmur best heard at the left sternal border, and increased pulmonary vascular markings on chest x-ray. Diagnose with an echocardiogram and close surgically.
- **Patent ductus arteriosus** becomes symptomatic in the first few days of life if it does not close spontaneously. There are bounding peripheral pulses and a continuous "machinery-like" heart murmur. Echocardiogram is diagnostic.
  - In premature infants who have not gone into heart failure, closure can be achieved with indomethacin.
  - In those that do not close, infants who are in heart failure, and full-term babies, surgical ligation via left thoracotomy or percutaneous endovascular closure is needed.

Clinical Pearl

If a baby goes home after birth and later develops cyanosis, the most likely diagnosis is tetralogy. If a baby is blue from infancy, the most likely diagnosis is transposition.

Right-to-left shunts share the presence of a murmur, diminished lung vascular markings in the lung, and cyanosis. Although 5 are always described (all beginning with the letter T), only the most common are typically are tested:

- **Tetralogy of Fallot** (4 abnormalities): VSD, pulmonary stenosis, overriding aorta, and right ventricular hypertrophy.
  - Although crippling, children do grow into infancy.
  - Children are small for their age, have a bluish hue in the lips and tips of their fingers, clubbing, and spells of cyanosis relieved by squatting ("Tet spells").
  - There is a systolic ejection murmur in the left third intercostal space, a small heart, diminished pulmonary vascular markings on chest x-ray, and EKG signs of right ventricular hypertrophy.
  - Echocardiogram is diagnostic; treatment is surgical repair.
- **Transposition of the great vessels** diagnosis is often made prenatally, and if not it becomes apparent shortly after birth due to severe cyanosis and failure to thrive. Children are kept alive by an ASD, VSD, or patent ductus (or a combination), but die very soon if not corrected. Suspect this diagnosis in a child age 1–2 days with cyanosis who is quite ill; perform an echocardiogram and proceed with urgent surgical repair.

Note

Tetralogy of Fallot is the most common cyanotic anomaly. On the exam, this is likely to be the answer for any question that asks about a cyanotic child age 5–6.

A 6-month-old girl has episodes of respiratory distress and audible stridor. She appears to be relieved when assuming a hyperextended position. The family has also noted mild difficulty in swallowing.

The combination of pressure on the esophagus and pressure on the trachea identifies a vascular ring. Barium swallow will show a typical extrinsic compression from the abnormal vessel. Bronchoscopy confirms the segmental tracheal compression and rules out diffuse tracheomalacia. Surgical repair is done by dividing the smaller of the double aortic arches.

During a school physical exam, a 12-year-old girl is found to have a heart murmur. She is referred for further evaluation. An alert cardiology fellow recognizes that she indeed has a pulmonary flow systolic murmur, but he also notices that she has a fixed split second heart sound. A history of frequent colds and upper respiratory infections is elicited.

This is a case of ASD. Echocardiography will establish the diagnosis. Close the defect percutaneously or with open surgery depending on size.

A 3-month-old boy is hospitalized for "failure to thrive." He has a loud, pansystolic heart murmur best heard at the left sternal border. Chest x-ray shows increased pulmonary vascular markings.

This is a classic description of a ventricular septal defect. Echocardiography is diagnostic, and surgical repair is indicated.

A 3-day-old premature baby has trouble feeding and pulmonary congestion. Physical examination shows bounding peripheral pulses and a continuous, machinery-like heart murmur. Shortly thereafter, the baby develops hypotension and tachycardia.

This vignette describes a child with a patent ductus arteriosus who has now progressed to heart failure. Echocardiography is diagnostic, and since he is progressing, surgical ligation is indicated (over pharmacological or catheter-directed closure).

A 3-day-old premature baby girl has mild pulmonary congestion, signs of increased pulmonary blood flow on x-ray, a wide pulse pressure, and a precordial machinery-like murmur. She is not in distress.

This vignette presents the same diagnosis of patent ductus arteriosus but without heart failure, and therefore less urgency. Being premature, this may be amenable to pharmacological closure with indomethacin.

A 6-year-old boy is brought to the United States by his new adoptive parents from an orphanage in Eastern Europe. The boy is small for his age and has a bluish hue in the lips and tips of his fingers. He has clubbing and spells of cyanosis relieved with squatting. He has a systolic ejection murmur in the left third intercostal space. Chest x-ray shows a small heart and diminished pulmonary vascular markings. EKG shows right ventricular hypertrophy.

Various scenarios are used to test tetralogy of Fallot, and this is a common variant where it is not recognized in infancy and progresses. The late presentation rules out Transposition, the next most common cyanotic defect. Confirm with an echocardiogram and repair surgically.

ACQUIRED HEART DISEASE

Aortic stenosis produces angina, syncope, and dyspnea. There is a harsh mid-systolic heart murmur best heard at the right second intercostal space and along the left sternal border. This is typically due to a congenitally bicuspid valve or progressive calcification of a tricuspid valve.

Clinical Pearl

Transcatheter aortic valve replacement (TAVR) is approved for high surgical risk patients, but otherwise standard open surgical valve replacement is the treatment of choice.

Start the workup with an echocardiogram. Surgical valvular replacement is indicated if there is a gradient >50 mm Hg, or at the first indication of CHF, angina, or syncope.

Chronic aortic insufficiency produces a wide pulse pressure ("water hammer pulse") and a blowing, high-pitched, diastolic heart murmur best heard at the second intercostal space and along the left lower sternal border. Patients are often followed with medical therapy for many years but should undergo valvular replacement at the first evidence of left ventricular dilatation on echocardiogram.

Acute aortic insufficiency due to endocarditis is seen in young drug addicts who suddenly develop heart failure and a new, loud diastolic murmur at the right second intercostal space. Emergency valve replacement and long-term antibiotics are needed.

Mitral stenosis is caused by a remote history of rheumatic fever. It presents with dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, cough, and hemoptysis. There is a low-pitched, rumbling diastolic apical heart murmur. As it progresses, patients become thin and cachectic and develop atrial fibrillation. Workup starts with echocardiogram. As symptoms become more disabling, mitral valve repair becomes necessary with a surgical commissurotomy or mitral valve replacement.

Clinical Pearl

MR is typically an indolent, progressive disease. However, a myocardial infarction can cause acute papillary muscle ischemia and acute MR, which is a cardiac surgical emergency.

Mitral regurgitation (MR) is most commonly caused by valvular prolapse but also can be caused by rupture of the chordae tendineae from a myocardial infarction. Patients develop exertional dyspnea, orthopnea, and atrial fibrillation. There is an apical, high-pitched, holosystolic heart murmur that radiates to the axilla and back. Workup and surgical indications are as above, with repair of the valve (annuloplasty) are preferred over prosthetic replacement.

Coronary artery disease (CAD) (**most common type of acquired heart disease in adults**) has a particularly high incidence in men age >45 and post-menopausal women. Risk factors include a history of smoking, sedentary lifestyle, hyperlipidemia, and type II diabetes.

Diagnosis is made with cardiac catheterization if there are indications of progressive, unstable, disabling angina. Percutaneous intervention (angioplasty, stent) is indicated for ≥70% stenosis; the presence of multivessel disease or single vessel disease involving the left main coronary artery are indications for surgical revascularization via coronary artery bypass grafting (CABG). Preferably, the patient should still have good ventricular function, as you cannot resuscitate dead myocardium. The left internal mammary artery is the primary conduit.

Postoperative care of heart surgery often requires that cardiac output be optimized. If cardiac output is considerably under normal (5 liters/min, or cardiac index 3), the pulmonary wedge pressure (or left atrial pressure, or left end-diastolic pressure) should be measured. Low numbers (0–3) suggest hypovolemia requiring volume resuscitation; high numbers (≥20) suggest ventricular failure requiring inotropy or mechanical support (e.g. intra-aortic balloon pump).

Chronic constrictive pericarditis produces dyspnea on exertion, hepatomegaly, and ascites, and shows a classic "square root sign" and equalization of pressures (right atrial, right ventricular diastolic, pulmonary artery diastolic, pulmonary capillary wedge, and left ventricular diastolic) on cardiac catheterization. Surgical pericardiectomy is curative.

A 72-year-old man has a history of angina and exertional syncopal episodes. He has a harsh midsystolic heart murmur best heard at the right second intercostal space and along the left sternal border.

This is a common presentation of aortic stenosis with the triad of angina, dyspnea, and syncope. Diagnose with echocardiogram. Surgical valvular replacement is indicated if gradient >50 mm Hg or at the first indication of CHF, angina, or syncope.

A 35-year-old woman has dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, cough, and hemoptysis. She has had these progressive symptoms for about 5 years. She looks thin and cachectic, and has atrial fibrillation and a low-pitched, rumbling diastolic apical heart murmur. At age 15 she had rheumatic fever.

This is more information than is likely to be provided on the exam but is classic for mitral stenosis. Start with an echocardiogram and eventually surgical mitral valve repair (or replacement) will be necessary.

A 55-year-old lawyer has progressive, unstable, disabling angina that does not respond to medical management. His father and 2 older brothers died of heart attacks at age 50. The patient stopped smoking 20 years ago but still has a sedentary lifestyle, is a bit overweight, has type II diabetes mellitus, and has high cholesterol.

This is a heart attack waiting to happen: this man needs a cardiac catheterization to see whether he is a suitable candidate for coronary revascularization, either percutaneous or surgical.

A 55-year-old lawyer has progressive, unstable, disabling angina that does not respond to medical management. His father and 2 older brothers died of heart attacks at age 50. The patient stopped smoking 20 years ago but still is a bit overweight and has a sedentary lifestyle, type II diabetes mellitus, and high cholesterol. Cardiac catheterization demonstrates 70% occlusion of 3 coronary arteries, with good distal vessels. His left ventricular ejection fraction is 55%.

The patient is lucky. He has good distal vessels (smokers and diabetics often do not) and enough cardiac function left. He clearly needs coronary artery bypass grafting. With triple-vessel disease, he is not a good candidate for a percutaneous intervention.

A 55-year-old lawyer is found to have coronary artery disease and undergoes a coronary artery bypass grafting. Postoperatively he is found to have a cardiac index 1.7 L/min/m^2 and left ventricular end-diastolic pressure of 3 mm Hg.

The postoperative management of open heart surgery is too esoteric for the exam, but a bit of applied physiology is not. Be able to recognize a dangerously low cardiac index without a high end-diastolic pressure, indicative of hypovolemia. Administer fluid.

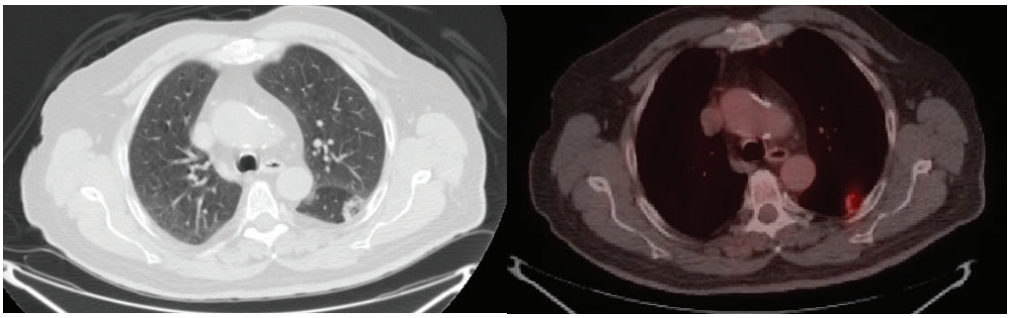
A 55-year-old lawyer is found to have coronary artery disease and undergoes a coronary artery bypass grafting. Postoperatively he is found to have a cardiac output 2.3 L/min. Pulmonary wedge pressure is 27 mm Hg.

Cardiac output is low but wedge pressure is high; this is left ventricular dysfunction. Support pharmacologically with inotropes; if not responsive, consider mechanical support such as an intra-aortic balloon pump.

PULMONARY

A **solitary "coin" lesion** found on chest x-ray has a significant chance of being malignant in people age >50, and even higher if there is a history of smoking.

- Seeking an older x-ray is always the first step when a solitary pulmonary nodule is detected: if the lesion is old, it needs continued interval surveillance; if it is new, it needs further evaluation starting with CT of the chest.
- CT findings and clinical characteristics will determine if further workup is necessary: high suspicion of lung cancer should proceed with a PET scan and then decision whether to obtain a biopsy.
  - If there is a PET-avid lesion in a smoker that is likely to be malignant, consider resection if a reasonable candidate; a false negative biopsy is not helpful.
  - An unclear clinical picture or poor surgical candidate should undergo biopsy via transbronchial fine needle aspiration for central lesions or transthoracic core needle biopsy for peripheral lesions. If unsuccessful, surgical wedge resection or biopsy via video-assisted thoracic surgery (VATS) may be necessary.
  - Factoring into this algorithm is the surgical candidacy of the patient. This includes age, functional status, comorbidities, cardiac disease, degree of lung impairment, and extent of disease and therefore the ability to cure.



Courtesy of Gary Schwartz, MD

Figure 5-1. CT and PET Scan Lung Nodule

Small-cell cancer of the lung is treated with chemotherapy and radiation, so assessment of operability and curative chances with surgery are not applicable. Operability and possibility of surgical cure apply only to non–small-cell cancer.

Clinical Pearl

Small-cell lung cancer is notorious for causing paraneoplastic syndromes; patients may present with Cushing syndrome, myasthenic crisis, and encephalitis, among other presentations.

- The operability of lung cancer is predicated on residual pulmonary function that would be left after resection. Determine how much lung would need to be resected (wedge resection, lobectomy, pneumonectomy) and measure baseline pulmonary function.
- Minimum residual FEV_1 of 800 mL is mandatory to undergo lung resection (less residual function could render the patient a pulmonary cripple—ventilator dependent but cured of cancer is not an acceptable outcome.)
- Alternative options for nonsurgical candidates include stereotactic beam radiotherapy with or without systemic chemotherapy.

The ability to cure lung cancer is directly related to stage. Staging is completed based on PET scan and sampling of mediastinal lymph nodes via endobronchial U/S-guided fine needle aspiration (EBUS-FNA) or surgical mediastinoscopy.

- **Stage I** disease is localized to the lungs and is cured by surgical resection.
- **Stage II** may have larger lesions or involve local nodes and are treated with surgical resection and adjuvant chemotherapy.
- **Stage III** relates to mediastinal lymph node involvement or very large tumors and can be cured in a subset of patients using a trimodal therapy: chemotherapy, radiotherapy, and surgical resection in some combination.
- **Stage IV** disease with distant metastases is not curable, so surgical resection is not an option.

> On a routine pre-employment physical examination, a chest x-ray is done on a 45-year-old chronic smoker. A solitary pulmonary nodule is found in the upper lobe of the right lung.

The concern, of course, is lung cancer. Look for an old x-ray to compare; otherwise start workup with a CT of the chest.

> A 65-year-old man with a 40-pack-year history of smoking presents with a chronic cough. Chest x-ray performed demonstrates a peripheral 2-cm solitary nodule not present on x-ray 1 year prior. CT reveals no mediastinal adenopathy, no calcification in the mass, and no other suspicious masses. Bronchoscopy and percutaneous needle biopsy have not been diagnostic. PET scan shows mild hypermetabolism in the mass and no other locations of uptake. He has good pulmonary function and is otherwise in good health.

In dealing with lung cancer there are 3 issues: diagnosis, ability to cure, and assessment of surgical candidacy. This man could tolerate a lung resection, which could be curative. Biopsy has been unsuccessful. A reasonable strategy would be a VATS wedge resection, and if it indeed is a cancer, completion lobectomy (lower long-term recurrence risk than a wedge resection alone).

Clinical Pearl

Immunotherapy is emerging as a valuable tool for advanced cancers that bear a genetic mutation; this option is unlikely to show up on the exam.

> A 72-year-old chronic smoker with severe chronic obstructive pulmonary disease (COPD) is found to have a central, hilar mass on chest x-ray. Bronchoscopy establishes a diagnosis of squamous cell carcinoma of the lung. His FEV_1 is 1.1L, and a ventilation/perfusion scan shows that 60% of his pulmonary function comes from the affected lung.

The history and physical exam suggested that the main limiting factor would be pulmonary function, so that issue was properly evaluated first. It takes an FEV_1 of at least 800 mL to survive surgery and not be a pulmonary cripple afterward. If this patient underwent a pneumonectomy—which he would need for a central tumor—he would be left with FEV_1 440 mL, which is not compatible with oxygen-free life. No further testing is necessary; he is not a surgical candidate and should be treated with some combination of radiation therapy, chemotherapy, and possibly immunotherapy.

> A 62-year-old chronic smoker has an episode of hemoptysis. Chest x-ray shows a central hilar mass. Bronchoscopy and biopsy establish a diagnosis of squamous cell carcinoma of the lung. His FEV_1 is 2,200 ml, and a ventilation/perfusion scan shows that 30% of his pulmonary function comes from the affected lung.

This patient could tolerate a pneumonectomy, but staging needs to be completed for the best treatment strategy. PET scan is the best noninvasive test for mediastinal or distant metastasis, followed by endobronchial ultrasound (EBUS) or surgical biopsy of mediastinal nodes if suspicious for cancer.

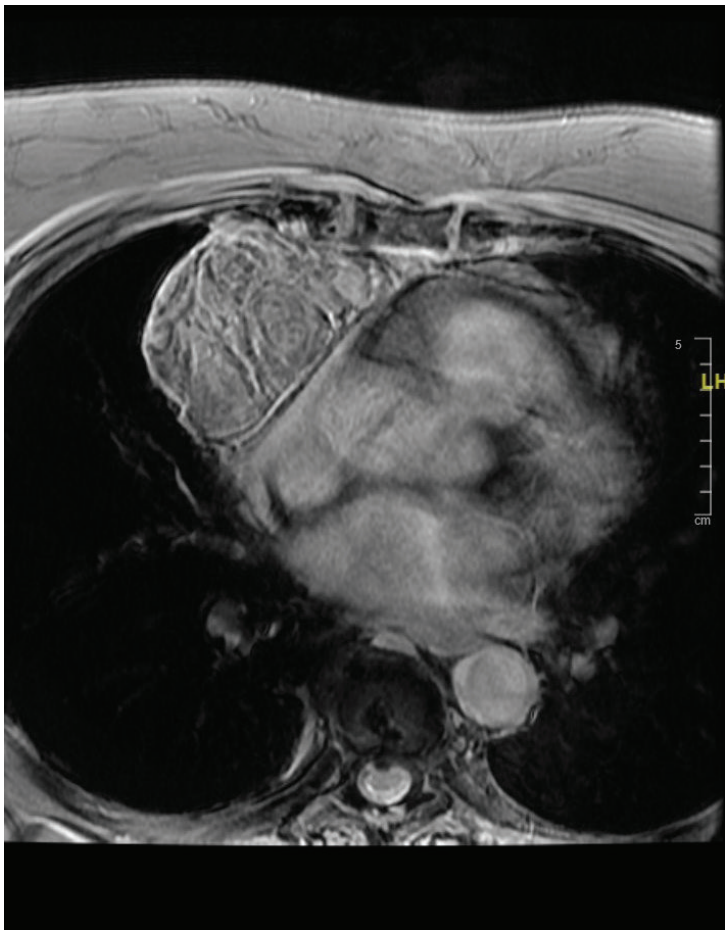
MEDIASTINUM

The mediastinum is divided into anterior, middle, and posterior compartments.

Tumors of the anterior mediastinum are easily remembered by the "4 Ts," each with discrete clinical and radiographic features.

- **T**hyroid (substernal goiter)
  - Typically extends from standard thyroid goiters, which are palpable.
  - Thyroid function testing and resection with or without upper sternotomy is indicated.
- **T**hymoma
  - Tends to be asymptomatic and incidentally discovered, but is also associated with myasthenia gravis.
  - Check for serum antibodies to anticholinesterase.
  - Thymectomy even in the absence of thymoma has been shown to improve quality of life in myasthenia and should be considered.
- "**T**errible" lymphoma
  - Typically presents in younger patients.
  - Symptoms tend to be systemic: fever, chills, night sweats, and weight change.

- Teratoma
  - Can be benign or malignant.
  - Measure serum tumor markers (AFP, HCG) prior to resection to surveil for future recurrence.



Courtesy of Gary Schwartz, MD

Figure 5-2. MRI Anterior Mediastinal Mass

The middle mediastinum includes the great vessels, the airway, and the esophagus. Masses in this location include aneurysms and malignancies, but benign congenital growths such as bronchogenic cysts also occur. Lymphadenopathy can also be present.

The posterior mediastinum is well known to harbor neurogenic tumors such as paraganglionic and nerve sheath tumors. MRI is necessary to evaluate for spinal cord involvement ("dumbbell tumor") and for surgical planning.

VASCULAR

Carotid artery stenosis is caused by atherosclerotic disease leading to progressive narrowing of the vessels. Flow limitation or plaque embolism can lead to transient ischemic attack (TIA) or frank cerebrovascular accident (CVA). Diagnosis is with U/S measuring diameter, as well as Doppler flow. Management includes lifestyle management (smoking, diet, exercise), antiplatelet therapy, and surveillance for progression. Symptomatic lesions and asymptomatic lesions with >70% stenosis should be repaired by surgical carotid endarterectomy (CEA).

Clinical Pearl

Carotid stenting has demonstrated good results with potentially fewer periprocedural complications, but for the exam, choose surgical repair.

Subclavian steal syndrome is rare but commonly tested. An arteriosclerotic stenotic plaque at the origin of the **left subclavian artery (proximal to the takeoff of the vertebral artery)** allows enough blood supply to reach the arm for normal activity, but does not allow enough to meet higher demands when the arm is exercised. When that happens, the arm diverts blood away from the brain by "reversing" blood flow in the vertebral artery.

Clinical presentation includes decreased brain perfusion and possible CNS symptoms (most commonly dizziness and even syncope):

- Claudication of the arm (coldness, tingling, muscle pain)
- Posterior neurologic signs (visual symptoms, equilibrium problems) when arm is exercised

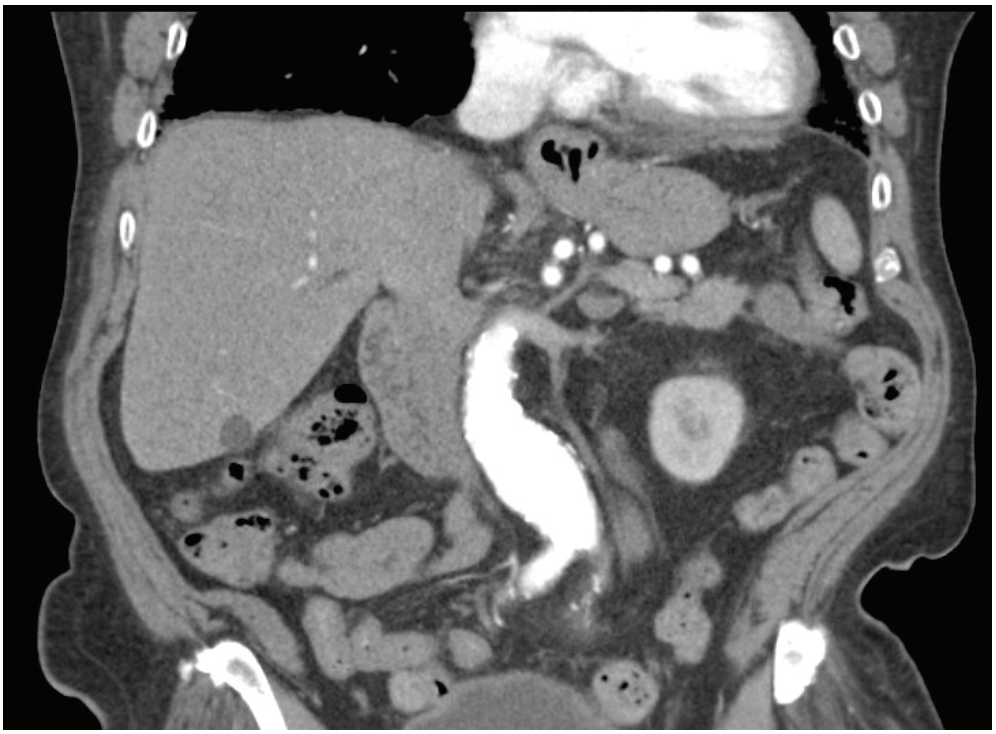
Vascular symptoms alone would suggest thoracic outlet syndrome, but the combination with neurologic symptoms identifies the subclavian steal. Duplex scan is diagnostic when it shows reversal of flow. Treatment is endovascular stenting (curative), or surgical bypass if that is not anatomically feasible.

Abdominal aortic aneurysm (AAA) is typically asymptomatic, presenting as a pulsatile epigastric abdominal mass on examination or found incidentally on imaging for another purpose. Size as measured by U/S or CT is the key to management, as well as the presence of symptoms (U/S is used for screening patients with hypertension and smoking; if you are thinking of aneurysm, begin with CT).

- If aneurysm $\leq$4 cm, it can be safely observed as chance of rupture is near zero.
- If aneurysm $\geq$5 cm, it should be electively repaired to prevent rupture.
- If aneurysm grows $\geq$1 cm per year during observation, it needs elective repair.
- If the abdomen is tender in the presence of a large or enlarging aneurysm, it is at risk for imminent rupture and needs urgent surgical repair. Similarly, new-onset back pain is concerning for an early rupture, with retroperitoneal bleeding causing the symptom.

Treatment is now endovascular stents inserted percutaneously. If that is not possible, do an open aneurysmectomy. Factors preventing an endovascular approach include specific anatomic criteria (neck of aneurysm, landing zone, and tortuosity of vascular tree) and available resources (angiography team/equipment). Surgical options include:

- Open surgical AAA repair using an interposition graft within the aneurysm sac (10–15% perioperative morbidity due to MI, renal failure, bowel ischemia)
- Emergency surgery for ruptured AAA (very high morbidity and mortality), although some of these have been treated with endovascular stents



Courtesy of Gary Schwartz, MD

Figure 5-3. CT Angiogram AAA Coronal

Arteriosclerotic occlusive disease of the lower extremities has an unpredictable natural history (except for the predictable negative impact of smoking), and so there is no role for "prophylactic" surgery in claudication.

- Lifestyle changes including smoking cessation and exercise are encouraged.
- Antiplatelet therapy is typically initiated, as is evaluation for other sites of atherosclerotic disease (e.g., coronary and carotid arteries).
- Surgery is done only to relieve disabling symptoms or to save the extremity from impending necrosis, i.e., when presenting with rest pain, which is the penultimate presentation prior to ulceration and frank gangrene.

When intermittent claudication becomes disabling, workup begins with a pulse exam, ankle-brachial index, and Doppler study looking for a pressure gradient that provides information about the location, level, and severity of an arteriosclerotic lesion.

- If there isn't a significant gradient, the disease is in the small vessels and not amenable to surgery.
- If there is a significant gradient, CT angiogram or MRA is performed to identify specific areas of stenosis or complete obstruction, and to locate good distal vessels to which a bypass graft could be anastomosed.

Treatment for short stenotic segments is angioplasty and stenting, but for more extensive disease the management is bypass graft, sequential stent, or longer stenting. When multiple lesions are present, proximal ones are usually repaired before distal ones are addressed.

Clinical Pearl

- Grafts originating at the aorta (aortobifemoral) and procedures on larger arteries are done with prosthetic material.
- Bypass between more distal vessels (femoropopliteal or beyond) is usually done with reversed saphenous vein grafts.

Clinical Pearl

Of the 6 Ps, **paralysis** is the most feared finding—and also typically the latest. The motor nerves are typically the most "resistant" to ischemia. Management should be initiated prior to progression to frank paralysis, or recovery is unlikely.

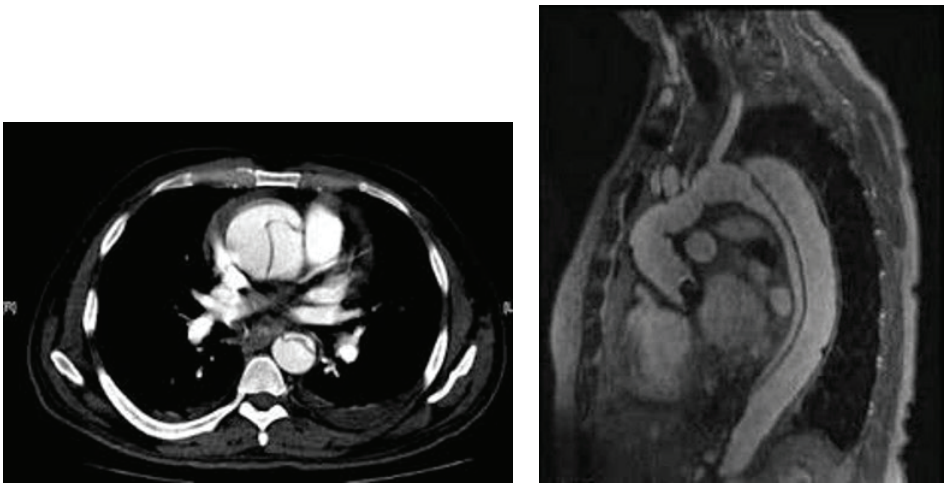
Arterial embolization from a distant source is seen in those with atrial fibrillation (a clot breaks off from the atrial appendage) or those with recent MI (the source of the embolus is the mural thrombus). Another source can be the aorta. The patient acutely develops the 6 Ps:

- **P**ain
- **P**aleness
- **P**oikilothermia
- **P**ulselessness
- **P**aresthesia
- **P**aralysis

Urgent evaluation and treatment should be completed within 6 hours because the likelihood of irreversible muscle and nerve injury increases after this time. Doppler study or CT angiogram will locate the point of obstruction. Early incomplete occlusion may be treated with thrombolytic therapy. Embolectomy with Fogarty catheters is effective for complete obstructions. Fasciotomy should be added if several hours have passed before revascularization in order to prevent compartment syndrome from reperfusion edema. Empiric heparin bolus should be given upon suspicion of this disease.

Dissection of the thoracic aorta is common in poorly controlled hypertensive patients. Clinical presentation resembles an MI, with sudden onset of extremely severe, tearing chest pain that radiates to the back and migrates down shortly after its onset. There may be unequal pulses in the upper extremities, and chest x-ray shows a widened mediastinum.

EKG and cardiac enzymes rule out an MI but confirm diagnosis with CT angiogram, magnetic resonance angiogram (MRA), or even transesophageal echocardiography (TEE). Type A dissection (involving the ascending aorta) is treated surgically, whereas type B (those in the descending only) is managed medically with control of the hypertension.



Courtesy of Gary Schwartz, MD

Figure 5-4. CT Angiogram Ascending Dissection and MRI Descending Dissection

A 54-year-old laborer who is right-handed notices coldness and tingling in the left hand, plus pain in the forearm when he does strenuous work. What really concerns him, however, is that in the last few episodes he also experienced transitory dizziness and blurred vision.

This presentation is concerning for subclavian steal syndrome. Claudication of the arm plus posterior brain neurologic symptoms is classic for this rare but fascinating condition. (It is often tested on the exam.) Duplex scan will demonstrate retrograde flow through the vertebral artery when the patient exercises the arm. Endovascular stenting or surgical bypass is curative.

A 62-year-old man has vague, poorly described epigastric and upper back discomfort. He is found on physical examination to have a 6-cm pulsatile mass deep in the abdomen between the xiphoid and the umbilicus. The mass is tender to palpation.

This is an abdominal aortic aneurysm that is beginning to leak. Get an immediate vascular surgery consultation, as urgent surgical repair is necessary.

A 68-year-old man is brought to the ED with excruciating back pain of 45 minute duration. He is diaphoretic and has systolic blood pressure 90 mm Hg. Examination reveals an 8-cm, pulsatile mass palpable deep in the abdomen, above the umbilicus.

Pain in the presence of an AAA is concerning; hemodynamic instability is life-threatening. This patient needs immediate emergency surgery.

A retired physician has claudication when walking more than 15 blocks.

Vascular surgical and endovascular interventions are palliative procedures; they do not cure arteriosclerotic disease. Claudication has an unpredictable course but is generally stable, so there is no indication for early operation or intervention. No workup is needed. If the patient smokes he should quit, and he would benefit from a program of exercise. Antiplatelet therapy may be helpful, and don't forget to work up for other sites of disease (coronary, carotid arteries).

A 56-year-old postal worker describes severe pain in his right calf when he walks 2–3 blocks. The pain is relieved by resting 10–15 minutes but recurs if he walks again the same distance. He cannot perform his job with this problem, but he does not yet qualify for retirement so he is most anxious to have this problem resolved. He does not smoke.

This patient needs help. Start with a pulse exam, ankle-brachial index, and Doppler study. If he has a significant gradient, do a CT angiogram or formal angiogram at the same setting of endovascular stenting or bypass grafting.

> A 56-year-old former smoker presents with pain in the right calf that keeps him from falling asleep. The pain goes away if he sits by the side of the bed and dangles the leg. His wife adds that she has watched him do that, and she has noticed that the leg, which was very pale when he was lying down, becomes deep purple several minutes after he is sitting up. On physical examination the skin of that leg is shiny, there is no hair, and there are no palpable peripheral pulses.

Pain at rest signifies an acutely threatened extremity. This patient needs a full workup to see whether a vascular intervention could help.

> A 65-year-old man presents to the ED with pain in his left lower extremity. The process began suddenly 2 hours ago. Physical examination reveals a cool extremity with no palpable pulses; pulse at the wrist is 95/min and irregular.

This scenario is highly concerning for an embolic event to the lower extremity, likely secondary to atrial fibrillation. This is a surgical emergency. Start systemic anticoagulation with heparin, and get the patient to the operating room ASAP for an embolectomy. If the ischemia has been ongoing for several hours, perform a fasciotomy.

> A 74-year-old man has sudden onset of extremely severe, tearing chest pain that radiates to the back and migrates down shortly after its onset. Blood pressure is 220/110 mm Hg and there are unequal pulses in the upper extremities. Chest x-ray reveals a wide mediastinum. EKG and cardiac enzymes are negative for myocardial infarction.

This is dissecting aneurysm of the thoracic aorta. Assuming renal function is normal, CT angiogram is the best study.

- If the aneurysm is in the ascending aorta, proceed to emergency surgery.
- If the aneurysm is in the descending aorta, admit to the ICU and proceed with IV management of hypertension.
- If there is evidence of compromised visceral perfusion (acidosis, renal failure), urgent surgical intervention is indicated.

Ulcers

Diabetic ulcer is typically indolent and located at pressure points (first metatarsophalangeal joint most commonly, secondly the calcaneus). It results from altered gait due to neuropathy with abnormal pressure points, and does not always heal because of the microvascular disease. Good blood glucose control and wound care can help, but it often becomes chronic and may require amputation due to osteomyelitis. Proceed with MRI to look for osteomyelitis and foreign body.

Ulcers from arterial insufficiency are usually as far away from the heart as possible, i.e., at the tip of the toes. They are generally pale and devoid of granulation tissue. The patient has other manifestations of arteriosclerotic occlusive disease (absent pulses, trophic changes, claudication, or rest pain). Workup begins with Doppler study looking for a pressure gradient, though in the presence of microvascular disease this may not be present (and these lesions are less amenable to surgery). Further evaluation with CT angiogram may be necessary and ultimately formal angiography leading to angioplasty, stenting, or surgical revascularization.

Venous stasis ulcers develop in chronically edematous, indurated, and hyperpigmented skin above the medial malleolus. The ulcer is painless, typically with a granulating bed. The patient often has varicose veins due to incompetent venous valves and suffers from frequent bouts of cellulitis. Duplex scan is useful in the workup.

Treatment revolves around physical support to keep the veins empty and avoid infection: support stockings, Ace bandages, and Unna compression boots. Surgery may be required (vein stripping, grafting of the ulcer, injection sclerotherapy); endovascular ablation with laser or radiofrequency may also be used.

A **Marjolin ulcer** is a SCC of the skin that has developed in a chronic leg ulcer. The classic setting is one of many years of healing and breaking down, such as seen in untreated third-degree burns that underwent spontaneous healing, or in chronic draining sinuses secondary to osteomyelitis. A dirty-looking, deeper ulcer develops at the site, with heaped up tissue growth around the edges. Biopsy is diagnostic. Treatment is wide local excision and skin grafting if necessary.

> A 67-year-old man with poorly controlled diabetes presents to his primary care doctor with a nonhealing ulcer on his heel. His hemoglobin A1C is 9.

Ulcer at a pressure point in a diabetic is caused by neuropathy, and once it has developed it is unlikely to heal due to microvascular disease. Goals of care are to keep the ulcer clean and prevent infection, which could result in osteomyelitis and ultimately require amputation. Improved glycemic control is mandatory although unlikely to reverse the damage. The other common location for diabetic foot ulcers is the first metatarsophalangeal joint.

> A 67-year-old man with hypertension and hyperlipidemia and a heavy smoking history presents with an ulcer at the tip of his left second toe. It is ecchymotic and insensate. There are no pulses palpable.

Lack of pulses is concerning for underlying vascular insufficiency, as ischemic ulcers present at the most distal points on the body. Management starts with local wound care and U/S to assess for a pressure gradient, followed by MRA or CT angiogram. Revascularization via endovascular stenting or surgical bypass may be possible and enable wound healing.

Clinical Pearl

You may not be able to completely heal a venous stasis ulcer, but the **most important** aspect of treatment is to **avoid infection**, which is exceedingly common and a frequent presentation of elderly patients in the ED.

A 40-year-old man has had a chronic draining sinus in his lower leg since he had an episode of osteomyelitis at age 12. In the last few months he has developed an indolent, dirty-looking ulcer at the site, with "heaped up" tissue growth at the edges.

"Heaped up" is a buzz word for SCC arising in a chronic wound (Marjolin ulcer). Biopsy is the first diagnostic step, and management is wide local excision (with subsequent skin grafting if necessary).

Coarctation of the aorta (CoA) may become symptomatic at any age, but typically it presents in youth with upper extremity hypertension and lower extremity hypotension or lack of palpable dorsal pulses. Chest x-ray shows scalloping of the ribs due to erosion from large collateral intercostal arteries, and CT angiogram is diagnostic. Treatment is surgical repair.

A 12-year-old boy undergoes a physical examination for his high school football team. He is found to have blood pressure 190/110 mm Hg on two separate evaluations. The remaining physical exam is normal, other than very faint dorsalis pedis pulses bilaterally.

This is a classic scenario describing coarctation of the aorta. An alternative question stem might include a chest x-ray with "scalloping" of the ribs. Diagnose with CT angiogram of the chest and repair surgically.

Pediatric Surgery 6

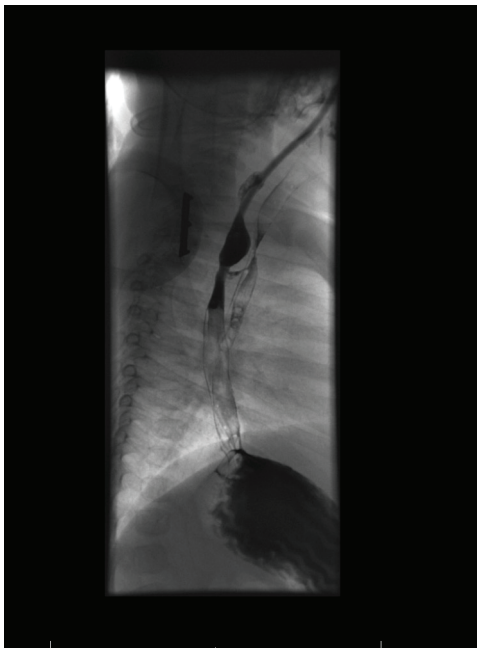
Learning Objectives

- ❑ Demonstrate understanding of common surgical problems in children within the first 24 hours of birth, within the first 2 months of life, and later in infancy
- ❑ Know the diseases thoroughly

FROM BIRTH TO FIRST 24 HOURS

Most congenital anomalies require surgical correction, but many occur in clusters; therefore, the presence of other anomalies must be assessed.

Esophageal atresia presents with excessive salivation noted shortly after birth or with choking spells when first feeding is attempted. A small NG tube is passed, and it will be seen coiled in the upper chest on x-ray. If there is normal gas pattern in the bowel, the baby has the most common form of the 4 types, in which there is a blind pouch in the upper esophagus and a fistula between the lower esophagus and the tracheobronchial tree.



Courtesy of Gary Schwartz, MD

Figure 6-1. Esophagram TEF

Note

The most important aspect of pediatric surgery is that the **diseases are congenital**. You cannot just "figure them out"; you must know them for the exam.

Before treatment begins, rule out associated anomalies: vertebral, anal, cardiac, tracheal, esophageal, renal, and radial (VACTER).

- Anorectal exam for imperforation
- X-ray for vertebral and radial anomalies
- Echocardiogram for cardiac anomalies
- U/S for renal anomalies

Initial surgical treatment is gastrostomy to provide nutrition and decrease aspiration. Once the child is healthier, then definitive surgical repair is performed.

Note

An important anatomical point is that even though the rectum may be only several millimeters from the imperforate skin, one cannot just "poke a hole."

Imperforate anus may be the clinical presentation noted on physical exam for the VACTER anomalies. If so, the others must be ruled out. Assess for a fistula to the vagina or perineum. If a fistula is present, repair can be delayed until further growth (but before toilet training). If no fistula is present, high rectal pouches must be temporarily diverted via a colostomy, whereas a blind pouch approaching the anus can be repair primarily ("pull-through").

Congenital diaphragmatic hernia is always on the left, and the defect results in the bowel herniating into the chest leading to a hypoplastic lung that ultimately retains its fetal-type circulation. Repair must be delayed 3–4 days to allow maturation. Babies often develop respiratory distress and need endotracheal intubation, low-pressure ventilation (careful not to hyperinflate the contralateral lung), sedation, and NG suction. Difficult cases may require extracorporeal membrane oxygenation (ECMO). U/S can diagnose (and occasionally repair) many babies in utero.

Gastroschisis and omphalocele present with a defect in the abdominal wall.

- In **gastroschisis**, the location of the umbilical cord is normal (it reaches the baby).
  - Defect is to the right of the cord (lateral), with no protective membrane
  - Bowel looks inflamed and matted, as if floating in amniotic fluid (which is very irritating)
  - **Clinical pearl: "sausage"**
- In **omphalocele**, the cord goes to the defect (central).
  - Defect has a thin membrane under which one can see a normal-looking bowel
  - **Clinical pearl: "spaghetti"**

Both of these conditions represent an open abdomen and thus mandate IV antibiotics.

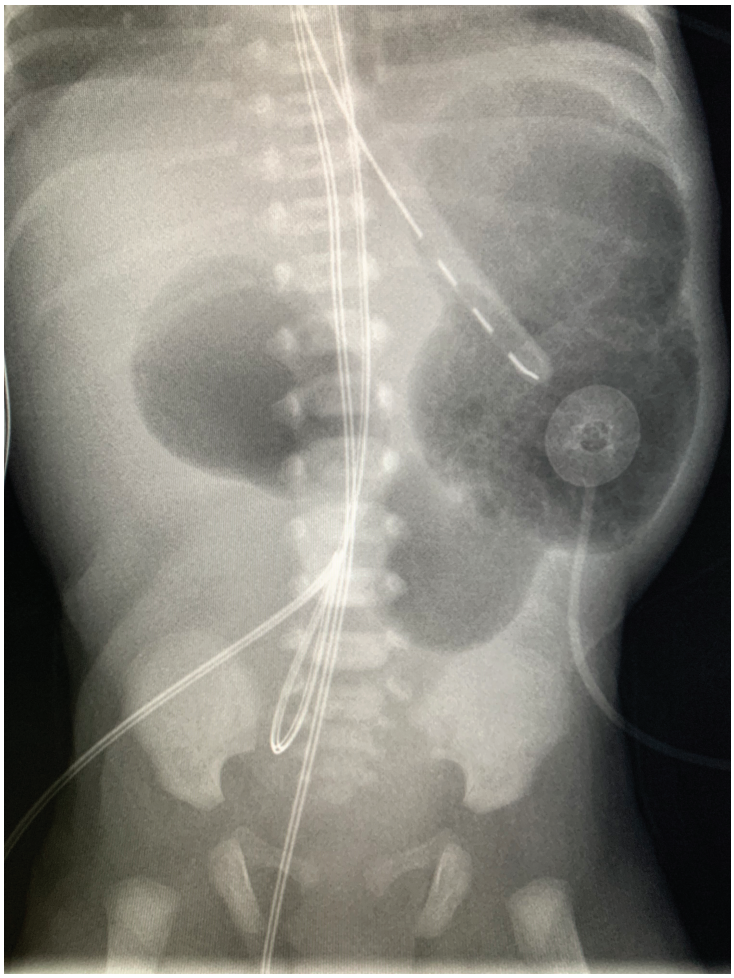
- Small defects can be closed primarily or with skin closure alone, leaving a ventral hernia to repair later when the child has grown.
- Large defects require construction of a prosthetic "silo" to house and protect the bowel. The contents of the silo are then manipulated into the peritoneal cavity over several days.

Babies with gastroschisis also need vascular access for parenteral nutrition because the inflamed bowel will not function normally for several weeks.

Exstrophy of the urinary bladder is also an abdominal wall defect of the lower abdominal wall, frequently associated with separation of the pubic symphysis and an exposed bladder and/or urethral mucosa. Delayed repair does not work, so surgical repair must be performed within the first 1–2 days of life.

Bilious vomiting in the newborn is strongly suggestive of a proximal intestinal obstruction. Bowel gas pattern on plain abdominal x-ray can provide important clues as to the underlying cause.

- Green vomiting and a "double bubble" on x-ray (a large air-fluid level in the stomach and a smaller one to its right in the first portion of the duodenum) are found in **duodenal atresia, annular pancreas, or malrotation**. The diagnosis is made definitively by surgical exploration. These anomalies all require surgical correction, but malrotation is the most dangerous because the bowel can become ischemic.
- If, in addition to the double bubble, there is some "typical gas pattern" beyond, the chances of malrotation are higher. Malrotation is diagnosed with contrast enema (safe, but not always diagnostic) or upper GI study (more reliable, but riskier due to potential for aspiration). Although described as a problem of the newborn, the first signs of malrotation can show up at any time within the first few weeks of life.
- Treatment for duodenal atresia and annular pancreas is commonly gastroduodenostomy or gastrojejunostomy. Treatment for malrotation is dividing the "Ladd bands" (just peritoneum) and an appendectomy, as the cecum is commonly not in the RLQ.



Courtesy of Gary Schwartz, MD

Figure 6-2. X-Ray Double Bubble

Clinical Pearl

In duodenal atresia, annular pancreas, and malrotation, the mother will have polyhydramnios (the child swallows the amniotic fluid and it is absorbed in the small bowel).

Intestinal atresia also shows up with green vomiting, but instead of a double bubble there are multiple air-fluid levels throughout the abdomen. There may be more than one atretic area, but no other congenital anomalies have to be suspected because this condition results from a vascular insufficiency in utero.

> Within 8 hours after birth, it is noted that a baby has excessive salivation. A small, soft nasogastric tube is inserted, and x-ray demonstrates the tube is coiled back on itself in the upper chest. There is air in the gastrointestinal tract.

This is the classic presentation of the most common type of tracheoesophageal (TE) fistula, with a proximal blind esophageal pouch and a distal TE fistula. First, rule out the associated anomalies (VACTER: vertebral, anal, cardiac, TE, and renal/radial). If no other anomalies, proceed with surgical repair.

> A newborn baby is found on physical examination to have an imperforate anus.

This is another part of the VACTER group, so rule out the other components. For the anal problem, if there is a fistula to the vagina or perineum repair can be safely done later, as the GI tract is not obstructed. If there is no fistula, barium enema will demonstrate the proximal level of the pouch: low imperforate anus can be corrected primarily; higher levels may need diverting colostomy and delayed repair.

> A newborn baby is found to be tachypneic, cyanotic, and grunting. The abdomen is scaphoid, and there are bowel sounds heard over the left chest. An x-ray confirms that there is bowel in the left thorax. Shortly thereafter, the baby develops significant hypoxia and acidosis.

Although most congenital diaphragmatic hernias are diagnosed prenatally, they can still present in extremis. The main problem is the hypoplastic lung. It is better to wait 36–48 hours to operate, in order to allow transition from fetal circulation to newborn circulation. Meanwhile, support the baby with supplemental oxygen, or even mechanical ventilation and nasogastric decompression.

> At the time of birth, it is noted that a child has a large abdominal wall defect to the right of the umbilicus. There is a normal cord, but protruding from the defect is a matted mass of angry-looking edematous bowel loops.

> A newborn baby is noted to have a shiny, thin, membranous sac at the base of the umbilical cord, with the cord entering the sac that contains liver and loops of normal bowel.

The first vignette is gastroschisis, the second one omphalocele. Quite simply, the bowel needs to be back in the abdomen and the abdomen closed; however, the "loss of domain" prevents immediate reduction. Therefore a silicon "silo" is used to house the bowel and gradually

return it to the abdomen. The baby with gastroschisis will also need vascular access for parenteral nutrition, as the bowel will not function normally for several weeks. Both will require IV antibiotics.

> Half an hour after the first feed, a baby vomits green fluid. X-ray demonstrates a large air-fluid level in the stomach and a smaller one in the first portion of the duodenum. There is air in the distal bowel, beyond the duodenum, in nondistended loops of bowel.

This represents bowel obstruction with 3 possible etiologies: duodenal atresia, annular pancreas, or malrotation. Upper GI study is diagnostic. Treatment is surgical repair.

> A newborn baby has green vomiting during the first day of life and does not pass any meconium. Except for abdominal distention, the baby is otherwise normal. X-ray demonstrates multiple air-fluid levels and distended loops of bowel.

This scenario is more consistent with intestinal atresia. Because it is caused by a vascular accident in utero, there are no other congenital anomalies to look for, but there may be multiple points of atresia.

FROM A FEW DAYS TO FIRST 2 MONTHS

Necrotizing enterocolitis is caused by bacterial invasion of the intestinal wall that develops in premature infants when they are first fed. There is feeding intolerance. Additionally, there is abdominal distention and rapidly developing thrombocytopenia (a sign of sepsis).

- Treatment is to stop all feedings and antibiotics, IV fluids, and parenteral nutrition.
- Surgical intervention is required if patients develop intestinal necrosis and perforation, which typically presents as abdominal wall erythema, air in the portal vein, intestinal pneumatosis, or pneumoperitoneum.

Unfortunately, resection of the involved bowel puts the child at risk for short gut syndrome, leading to malnutrition and the need for lifelong total parenteral nutrition. However, bowel resection is lifesaving and must be undertaken immediately to prevent further sepsis and death.

Meconium ileus is caused by abnormally thick meconium with resultant intestinal obstruction, typically seen in babies who have cystic fibrosis (often suspected due to by family history). There is feeding intolerance and bilious vomiting.

- X-ray shows multiple dilated loops of small bowel and a ground-glass appearance in the lower abdomen.
- Gastrografin enema is both diagnostic (microcolon and inspissated pellets of meconium in the terminal ileum) and therapeutic (gastrografin draws fluid in and dissolves the pellets).

Hypertrophic pyloric stenosis presents at age ~3 weeks, more commonly in first-born boys. There is nonbilious projectile vomiting after each feeding. The baby is hungry and eager to eat again after he vomits.

Clinical Pearl

The metabolic derangement is the same pathophysiology as adults, with extensive vomiting, as reviewed in the fluids and electrolytes section. Resuscitate with crystalloid and supplemental potassium before proceeding to surgery.

By the time patients receive medical attention they tend to be dehydrated, with visible gastric peristaltic waves and a palpable "olive-size" mass in the RUQ. If the mass cannot be felt, U/S is diagnostic. Treatment is rehydration and correction of the hypochloremic, hypokalemic metabolic alkalosis, followed by pyloromyotomy.

Biliary atresia should be suspected in infants age 6–8 weeks who have persistent, progressively increasing jaundice (which includes a substantial conjugated fraction). Check viral serologies and sweat test to rule out other problems (e.g., cystic fibrosis), and do a HIDA scan after 1 week of phenobarbital (a powerful choleretic).

If no bile reaches the duodenum even with phenobarbital stimulation, surgical exploration is needed.

- Surgical repair is long-lasting in 1/3 of patients.
- Surgical repair is short-lived in 1/3 of patients, who ultimately require liver transplantation.
- Liver transplantation is required immediately in 1/3 of patients.

Hirschsprung disease (aganglionic megacolon) is a functional physiologic obstruction of the bowel that can be recognized in early life or may go undiagnosed for many years. The cardinal symptom is chronic constipation.

- With short segments, rectal exam may lead to explosive expulsion of stool and flatus, with relief of abdominal distention.
- In older children in whom the differential diagnosis with psychogenic problems is an issue, the presence of fecal soiling suggests the latter.
- X-ray demonstrates distended proximal colon (the uninvolved portion) and "normal-looking" distal colon, which is the aganglionic part.
- Diagnosis is made with full-thickness biopsy of rectal mucosa looking for the absence of ganglia.
- Initial treatment is usually colostomy in order to optimize general health (nutrition, etc.), and then once "healthy," a "pull-through" definitive procedure.

A 4-day old premature baby is born with a patent ductus arteriosus (PDA) and treated with indomethacin. On day 14 of leave, he develops feeding intolerance, abdominal distention, and a platelet count of 30K.

The PDA has nothing to do with the current problem; this information only stresses that prematurity puts babies at risk for multiple problems. The PDA can be treated medically or surgically (via angiographic methods) as indicated (see the congenital heart surgery section). The problem now is necrotizing enterocolitis. Stop all feedings and start broad-spectrum antibiotics, IV fluids, and parenteral nutrition. Surgical intervention may be needed if the baby develops abdominal wall erythema, air in the portal vein, or pneumoperitoneum signifying bowel perforation.

> A 3-day-old, full-term baby is brought in because of feeding intolerance and bilious vomiting. X-ray demonstrates multiple dilated loops of small bowel and a ground-glass appearance in the lower abdomen. The mother has cystic fibrosis.

The family history and clinical presentation are consistent with meconium ileus. Gastrografin enema may be both diagnostic and therapeutic, so it is the obvious first choice. If unsuccessful, surgery may be needed. If the baby does indeed have cystic fibrosis, management of the other manifestations of the disease will also be necessary.

> A 3-week-old baby has had "trouble feeding" and is not gaining weight. He presents with bilious vomiting, and x-ray demonstrates a "double bubble" with a normal gas pattern distally.

This was reviewed in the first section but repeated here, as it can show up at any point in the first few weeks of life: malrotation. Proceed with upper GI series and likely surgical exploration.

> A 3-week-old first-born, full-term baby boy began to vomit 3 days ago. The vomiting is projectile and nonbilious, and occurs after each feeding. The baby is hungry and eager to eat again after he vomits. An olive-size mass is palpable in the right upper quadrant.

This is a straightforward description of hypertrophic pyloric stenosis. Check electrolytes, which will likely demonstrate a hypokalemic, hypochloremic metabolic alkalosis. Rehydrate and correct potassium, then proceed to the operating room for pyloromyotomy.

> A 2-month-old baby boy is brought to the pediatrician due to chronic constipation. He has abdominal distention, and abdominal x-ray demonstrates gas in dilated loops of bowel throughout the abdomen. Rectal examination is followed by explosive expulsion of stool and flatus, with remarkable improvement of the distention.

This scenario is suspicious for Hirschsprung disease (aganglionic megacolon). Barium enema will define the normal-looking aganglionic distal colon and the abnormal-looking, distended, normal proximal colon, but the diagnosis is established with full thickness biopsy of the rectal mucosa to look for the **absence of ganglia**. Definitive surgical repair is usually performed after initial diverting colostomy.

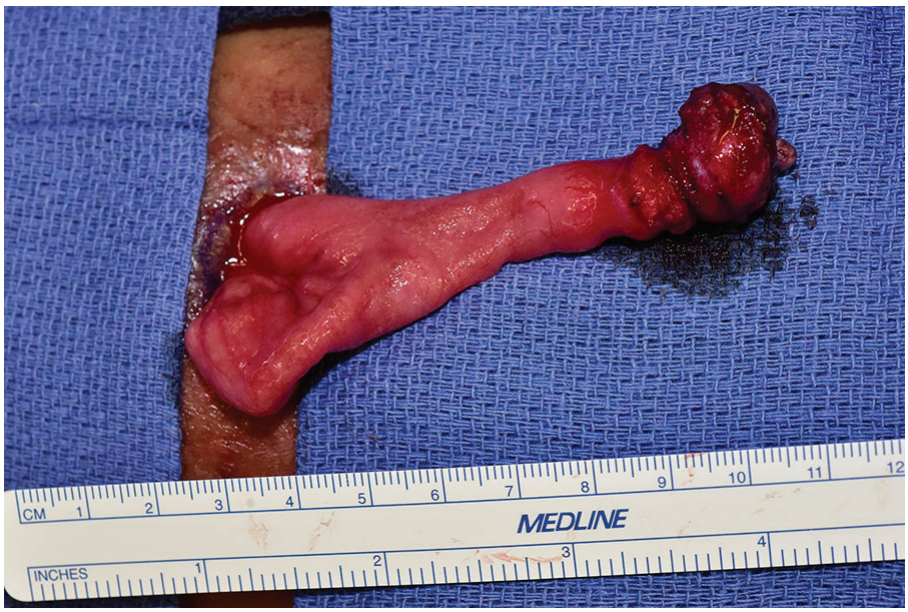
LATER IN INFANCY

Intussusception occurs in chubby, healthy babies age 6–12 months, who have episodes of colicky abdominal pain that make them draw their knees up to their chest.

- The pain lasts for ~1 minute, and the child looks perfectly happy and normal until the next episode.
- Physical exam may reveal a vague mass on the right side of the abdomen or an "empty" RLQ.

- Parents may describe stools as "currant jelly" (stool mixed with blood, mucous and sloughed epithelium).
- Barium or air enema is both diagnostic and often therapeutic.
- If complete reduction is not achieved radiologically (seeing reflux in the terminal ileum) or if it recurs, surgery is indicated.

Meckel's diverticulum should be suspected in lower GI bleeding in the pediatric age group. Diagnose with a radioisotope scan looking for gastric mucosa in the lower abdomen, and perform a small bowel resection. Recall the rule of 2s, where this condition usually occurs before age 2 years and within 2 feet of the ileocecal valve. The bleeding results from ulceration of the abnormal gastric mucosa.



Courtesy of Gary Schwartz, MD

Figure 6-3. Meckel's Diverticulum

Child abuse should always be suspected when injuries cannot be properly accounted for. Some classic presentations include:

- Subdural hematoma plus retinal hemorrhages (shaken baby syndrome)
- Multiple fractures in different bones at various stages of healing
- All scalding burns particularly burns of both buttocks and burns with distinct lines of demarcation

Refer to the proper authorities, but before doing so make certain it is indeed abuse and not a very unusual experience. Once the call is made, it is irreversible until a judge intervenes.

A 9-month-old boy is brought to the pediatrician due to episodes of abdominal pain that are severe but intermittent. His mother reports bloody stools but states he is otherwise very healthy and happy.

Intussusception is the most likely diagnosis. Barium or air enema are both diagnostic and therapeutic in most cases. If reduction is not achieved radiologically with reflux in the terminal ileum, then surgery is necessary.

A 7-year-old boy passes a large bloody bowel movement.

GI bleed in this age group is a Meckel's diverticulum until proven otherwise. Diagnose with a radioisotope scan looking for gastric mucosa in the lower abdomen and manage surgically.

A 1-year-old child is brought in with second-degree burns of both buttocks. The stepfather relates that the child fell into a hot tub.

This pattern of burn is suspicious for child abuse.

Eye, Ear, Nose, and Throat Surgery 7

Learning Objectives

- ❑ List the common ophthalmological conditions and procedures, with indications, complications, and alternatives
- ❑ Describe the common head and neck masses and their prognoses and management
- ❑ List the presenting features, diagnosis, and management of ENT emergencies

EYE (OPHTHALMOLOGY)

Pediatric Ophthalmology

Amblyopia is a vision impairment caused by interference with the processing of images by the brain during the first 6 or 7 years of life. The most common expression of this phenomenon is the child with strabismus (dysconjugate gaze, so-called "wandering eye"). Faced with 2 overlapping images, the brain suppresses one of them. If the strabismus is not corrected early on, there will be permanent cortical blindness of the suppressed eye, even though the eye is structurally normal. Should an obstacle impede vision in one eye during those early years (for instance, a congenital cataract), the same problem will develop.

Strabismus is verified by showing that the reflection from a light comes from different areas of the cornea in each eye. Strabismus should be surgically corrected when diagnosed to prevent the development of amblyopia. When reliable parents relate that a child did not have strabismus in the early years but develops it later in infancy, the problem is an exaggerated convergence caused by refraction difficulties. In that case corrective glasses instantly resolve the problem. True strabismus does not resolve spontaneously.

A **white pupil in a baby** is an ophthalmologic emergency, as it may be caused by a retinoblastoma. Even if the white pupil is caused by a less lethal problem like a congenital cataract, it should be addressed urgently to in order to prevent amblyopia.

Adult Ophthalmology

Glaucoma is a very common source of blindness, but because of its silent nature it is unlikely to be discovered by routine exam. **Acute closed-angle glaucoma** (a variant) presents as very severe eye pain or a frontal headache, typically starting in the evening when the pupils have been dilated for several hours, e.g., watching television in a dark room; it may be associated with seeing halos.

- On physical exam the pupil is dilated and does not react to light, the cornea is cloudy with greenish hue, and the eye feels "hard as a rock."
- Emergency surgery is required to decompress fluid trapped in the anterior chamber.
- While waiting for ophthalmologist, administer systemic carbonic anhydrase inhibitors (e.g., acetazolamide) and apply topical beta-blockers and alpha-2–selective adrenergic agonists (alternatively, mannitol and pilocarpine).

Orbital cellulitis is an ophthalmologic emergency that presents with tender, red, and swollen eyelids. Patients tend to be febrile, but the key finding when the eyelids are pried open is that the pupil is dilated and fixed and ocular motion is very limited, potentially with pus in the orbit. Diagnosis is clinical, but CT is necessary for surgical planning; proceed with emergency surgical drainage. They will require IV antibiotics as well.

Chemical burns of the eye require massive irrigation, as is required anywhere on the body. Start irrigation with plain water as soon as possible, and do not wait until arrival at the hospital. Once the eye has been pried open and washed under running water for about 30 minutes, get the patient to the ED. At the hospital, irrigation with saline is continued, and corrosive particles are removed from hidden corners.

Note

Anywhere on the body and ingested, alkaline burns are worse than acid burns.

Before the patient is sent home, pH is tested to assure that no harmful chemicals remain in the conjunctival sac.

Retinal detachment is another emergency that presents with flashes of light and "floaters." The number of floaters gives a rough idea of the magnitude of the problem: 1 or 2 floaters may only have vitreous tugging at the retina with little actual detachment, whereas dozens of floaters ("snow storm") may have a larger piece of the retina pulled away and there is risk for detachment of the remaining retina. Emergency intervention with laser "spot welding" will protect the remaining retina.

Note

Any neurologic abnormality must have CVA ruled out first.

Embolic occlusion of the retinal artery is also an emergency, although little can be done about it. The patient (typically elderly) describes sudden loss of vision from one eye; within 30 minutes the damage will be irreversible, but the standard recommendation is for the patient to breathe into a paper bag and have someone repeatedly press hard on the eye and release while he is in transit to the ED, in order to vasodilate and shake the clot into a more distal location so that a smaller area becomes ischemic.

Newly diagnosed diabetics need ophthalmologic evaluation if they have type II because they may have had it for years before diagnosis was made. Retinal damage may have already occurred, and proper treatment may prevent its progression. Young people diagnosed with type I often develop eye problems after 20+ years of living with diabetes.

> A young mother is visiting your office for routine medical care. She happens to have her 18-month-old baby with her, and you happen to notice that one of the pupils of the baby is white, whereas the other one is black.

An ophthalmologic and potentially life-and-death emergency. A white pupil (leukocoria) at this age can be due to a retinoblastoma. This child needs to see the ophthalmologist immediately. If it turns out to be something more innocent, like a cataract, it still needs correction to avoid amblyopia.

> A 53-year-old woman arrives at the ED complaining of extremely severe frontal headache and nausea. The pain started about an hour ago, shortly after she left the movies where she watched a double feature. On further questioning she reports seeing halos around the lights in the parking lot when she left the theater. On physical examination the pupils are mid-dilated and do not react to light. The corneas are cloudy with a greenish hue, and the eyes feel hard.

This is a classic description of acute glaucoma. Although most are asymptomatic, this requires immediate treatment. Treat with systemic carbonic anhydrase inhibitors, topical beta-blockers, and alpha-2–selective adrenergic agonists while awaiting an ophthalmologist for surgical drainage.

> A 32-year-old woman presents in the ED with swollen, red, hot, tender eyelids on the left eye. She has fever and leukocytosis. When prying the eyelids open you can ascertain that her pupil is dilated and fixed and that she has very limited motion of that left eye.

This scenario is obviously describing an infectious problem, and orbital cellulitis is an ophthalmologic emergency. Start with a CT to assess the extent of the orbital infection and begin IV antibiotics

> A frantic mother reaches you on the phone, reporting that her 10-year-old boy accidentally splashed drain remover on his face. He is screaming in pain, complaining that his right eye hurts terribly.

Copious irrigation is the main treatment for chemical burns. The point of this vignette is to remind you that time is a key element. If the mother is instructed to bring the boy to the ED, his eye will be cooked to a crisp by the time he arrives. The correct answer here is to instruct the mother to pry the eye open under cold water from the tap at home and irrigate for 30 minutes before bringing the child to the hospital. You will do more irrigation in the ED, remove solid matter, and eventually recheck the pH before the child goes home.

> A 59-year-old, myopic gentleman reports "seeing flashes of light" at night when his eyes are closed. Further questioning reveals that he also sees "floaters" during the day that number 10 or 20. He also sees a cloud at the top of his visual field.

This description if very concerning for retinal detachment; the frequency of "floaters" is an ominous sign. The "cloud" at the top of the visual field is hemorrhage settling at the bottom of the eye. This is another ophthalmologic emergency that requires laser treatment to "spot weld" the retina and prevent further detachment.

A 77-year-old man suddenly loses sight from the right eye. He calls you on the phone 10 minutes after the onset of the problem. He reports no other neurologic symptoms.

The acute onset is typical of an embolic occlusion of the retinal artery. First clinically evaluate for a CVA. If negative, this is an ophthalmologic emergency, although little can be done. Get the patient to the ED immediately. It might help for him to take an aspirin and breathe into a paper bag en route and have someone press hard on his eye and release it repeatedly.

A 55-year-old man is diagnosed with type II diabetes mellitus. On questioning about eye symptoms, he reports that sometimes after a heavy dinner the television becomes blurry and he has to squint to see it clearly.

The blurry TV is no big deal: the lens swells and shrinks in response to swings in blood sugar. The important point is that he needs to start getting regular ophthalmologic follow-up for retinal complications. It takes 10–20 years for these to develop, but type II diabetes may be present that long before it is diagnosed.

EAR, NOSE, AND THROAT (OTOLARYNGOLOGY)

Neck Mass

Neck mass can be congenital, inflammatory, or neoplastic.

- **Congenital** masses (seen in young people) are typically present for years before they become symptomatic (get infected).
- **Inflammatory** masses are typically measured in days or weeks, after which they typically resolve.
- **Neoplastic** masses typically present with several months of relentless growth.

Congenital

A **thyroglossal duct cyst** is a 1–2 cm neck mass located in the midline at the level of the hyoid bone that originates from the foramen cecum in the tongue (pulling at the tongue retracts the mass). Surgical removal includes the cyst, the middle segment of the hyoid bone, and the track that leads to the base of the tongue (Sistrunk procedure). You must also make certain that the patient has a thyroid gland, as sometimes the only thyroid tissue is in the cyst.

A **branchial cleft cyst** occurs laterally, along the anterior edge of the sternomastoid muscle, anywhere from in front of the tragus to the base of the neck. It is typically several centimeters in diameter and sometimes has a punctate opening and blind tract in the skin overlying it.

Cystic hygroma is a lymphatic overgrowth malformation made up of **normal lymphatics** found at the base of the neck as a large, spongy, ill-defined mass that occupies the entire supraclavicular area and seems to extend deeper into the chest. In fact, they often extend into the mediastinum; therefore CT is necessary prior to surgical excision.

Inflammatory and Neoplastic

The vast majority of recently enlarged lymph nodes are benign, so an extensive workup should not be undertaken right away. Complete history and physical should be followed by reevaluation in several weeks; if the mass is still there, further workup is necessary.

A persistently solitary enlarged **lymph node** (over weeks or months) could still be inflammatory, but neoplasia has to be ruled out. There are several patterns that are suggestive of specific diagnosis:

Lymphoma is typically seen in young people; they often have **multiple enlarged nodes** (in the neck and elsewhere) and have been suffering from low-grade fever and night sweats. FNA can be done, but usually a node has to be surgically removed for flow cytometry to determine specific subtype. Chemotherapy is the usual treatment.

Metastatic cancer that has spread to supraclavicular nodes invariably comes from below the clavicles, not from the head and neck. Lung or intra-abdominal tumors are the usual primaries. Biopsy of the lymph node may help establish a tissue diagnosis. It is commonly on the left side (Virchow's node), close to where the thoracic duct empties into the left subclavian-internal jugular vein junction.

SCC of the mucosa of the head and neck is seen in older men who smoke, drink, and have rotten teeth, as well in those with immunocompromised states such as HIV. Often the first manifestation is a metastatic node in the neck (typically to the jugular chain). The ideal diagnostic workup is a triple endoscopy ("panendoscopy") looking for the primary tumor; if found, biopsy will confirm the diagnosis and CT will demonstrate the extent. Ideally avoid biopsy of the node, as an incision in the neck may interfere with the appropriate surgical approach for the tumor. If no primary lesion is identified on panendoscopy, FNA of the node is the best step to obtain a tissue diagnosis. Treatment involves surgical resection, radical lymph node dissection, and very often radiotherapy and platinum-based chemotherapy.

Clinical Pearl

Other presentations of SCC include persistent hoarseness, persistent painless ulcer in the floor of the mouth, or persistent unilateral earache.

Acoustic neuroma should be suspected in an adult with unilateral sensory hearing loss. MRI is the best diagnostic modality. Make certain the patient was not involved in unilateral loud noise (e.g., firearm shooting).

Facial nerve tumors produce gradual unilateral facial nerve paralysis affecting both the forehead and the lower face, as opposed to sudden onset paralysis, which suggests Bell's palsy (but a **CVA must be ruled out**). Gadolinium-enhanced MRI is the best diagnostic study.

Parotid tumors typically present as visible and palpable in front of the ear or around the angle of the mandible. Most are pleomorphic adenomas ("mixed" tumors), which produce no pain or facial nerve paralysis. A hard parotid mass that is painful or produces paralysis is likely a parotid cancer.

- Resect with a normal tissue margin via superficial parotidectomy due to the potential for malignant degeneration.
- FNA may be done, but open biopsy is absolutely contraindicated.

In malignant parotid tumors, the facial nerve is sacrificed and a nerve interposition graft performed.

A 15-year-old girl has a round, 1-cm cystic mass in the midline of her neck at the level of the hyoid bone. When the mass is palpated while the tongue is pulled, there seems to be a connection between the two. The mass has been present for at least 10 years, but only recently bothered the patient because it got infected.

This is a typical presentation of a thyroglossal duct cyst. Management is surgical via the Sistrunk procedure: removal of the mass and the track to the base of the tongue, along with the medial segment of the hyoid bone. On the exam it is unlikely that all of these features will be present, but the midline location is the key. Make certain that the patient has a thyroid gland, as the only thyroid tissue may be in the cyst.

An 18-year-old woman has a 4-cm, fluctuant round mass on the side of her neck, just beneath and anterior to the sternocleidomastoid. She reports that it has been there at least 10 years, although she thinks that it has become somewhat larger in the last year or two. A CT shows the mass to be cystic.

This can be a branchial cleft cyst. Elective surgical removal is indicated.

A 6-year-old girl has a mushy, fluid-filled mass at the base of her neck that has been noted for several years. The mass is ~6 cm in diameter, occupies most of the supraclavicular area, and seems by physical examination to go deeper into the neck and chest.

A common description of a cystic hygroma. Perform a CT to see how deep the mass goes into chest to plan surgical resection.

A 22-year-old woman notices an enlarged lymph node in her neck. The node is in the jugular chain, measures ~1.5 cm, is not tender, and was discovered by the patient yesterday. The rest of the history and physical examination are unremarkable.

Give it some time before pursuing a complicated workup, as this may be simple lymphadenitis. Schedule the patient to be rechecked in 2–3 weeks. If the node has gone away by then, it was inflammatory and nothing further is needed. If it's still there, it could be neoplastic and FNA should be performed for further information. A few weeks of delay will not significantly impact the overall course of a neoplastic process.

A 22-year-old woman presents with an enlarged lymph node in her neck. The node is in the jugular chain, measures ~2 cm, is firm, is not tender, and was discovered by the patient 6 weeks ago. There is a history of low-grade fever and night sweats for the past 3 weeks. Physical examination reveals mildly enlarged lymph nodes in the axilla and left groin.

The presence of systemic symptoms and multistation lymphadenopathy in this age group is highly suspicious for lymphoma. Tissue diagnosis will be needed; start with FNA of the most accessible node, but typically excisional lymph node biopsy is necessary for flow cytometry to subtype the malignancy and guide choice of chemotherapy.

> A 72-year-old former smoker presents with a 3-cm hard mass in the left supraclavicular region. The mass is movable and not tender and has been present for 3 months. The patient has had a 20-pound weight loss in the past 2 months but denies fever or night sweats.

"Virchow's node" describes a supraclavicular site of metastases, typically from chest or abdominal primary cancers. Biopsy the node to diagnose the primary cancer, but the presence of this node represents metastatic disease (stage IV).

> A 69-year-old former smoker presents with a hard, fixed, 4-cm mass in his neck. The mass is just medial and is in front of the sternocleidomastoid muscle, at the level of the upper notch of the thyroid cartilage. It has been there for several months and is growing.

The age, smoking history, and location all point to metastatic SCC to a jugular chain node from a primary in the mucosa of the head and neck. The best diagnostic approach is panendoscopy, with biopsy of any identifiable lesions. CT will establish extent and operability. Treatment is multimodal: radiation, platinum-based chemotherapy, and surgery if possible. Other potential presentations on the exam include hoarseness, oral ulcers, and earache, especially in heavy smokers and HIV patients.

> A 52-year-old man complains of hearing loss. When tested he is found to have unilateral sensory hearing loss on one side only. He does not engage in any activity (such as sport shooting) that would subject that ear to noise that spares the other side.

Unilateral versions of common ENT problems in the adult suggest malignancy—in this case, acoustic neuroma. Note that if the hearing loss had been conductive, a cerumen plug would be the most likely diagnosis. Physical examination followed by MRI of the head is diagnostic.

> A 56-year-old man develops slow, progressive paralysis of the facial nerve on one side. It took several weeks for the full-blown paralysis to become obvious, and it has been present now for 3 months. It affects both the forehead and the lower face.

Gradual, unilateral nerve paralysis suggests a neoplastic process. Diagnose with MRI.

> A 45-year-old man presents with a 2-cm firm mass in front of the left ear, which has been present for 4 months. The mass is deep to the skin, and it is painless. The patient has normal function of the facial nerve.

Pleomorphic adenoma ("mixed" tumor) of the parotid does not typically involve the facial nerve and therefore does not present with neurological findings. FNA may be appropriate, but the point of the exam question will be to *not* biopsy the mass via an open approach; superficial parotidectomy is used for both diagnosis and treatment.

A 65-year-old man presents with a 4-cm hard mass in front of the left ear that has been present for 6 months. The mass is deep to the skin, and it is fixed. He has constant pain in the area, and for the past 2 months has had gradual progression of left facial nerve paralysis. He has rock-hard lymph nodes in the left neck.

In contrast to the previous vignette, this mass has caused neurological deficits in the facial nerve territory and is most suspicious for parotid cancer. He will need total parotidectomy with facial nerve reconstruction.

Emergencies and Miscellaneous

Ludwig's angina is an abscess of the floor of the mouth, often as the result of a dental infection. The usual findings of an abscess are present, but the special issue here is the threat to the airway that arises from swelling of the tongue. Incision and drainage are done, but intubation and tracheostomy may also be needed to protect the airway.

Bell's palsy produces sudden paralysis of the facial nerve for no apparent reason. Although not an emergency per se, current practice includes the use of antiviral medications—and as is the case for other situations in which antivirals are used, prompt and early administration is the key to their success. Steroids are also typically prescribed. First rule out stroke prior to treating for Bell's palsy.

Facial nerve injuries sustained in trauma produce paralysis right away. Patients who have normal nerve function at the time of admission and later develop paralysis are likely to have swelling that will resolve spontaneously.

Cavernous sinus thrombosis is heralded by the development of diplopia (secondary to paralysis of extrinsic eye muscles) in a patient suffering from frontal or ethmoid sinusitis. This is a serious emergency that requires hospitalization, CT scan, IV antibiotics, and drainage of the affected sinuses.

Epistaxis in children is typically from nose-picking; the bleeding comes from the anterior septum, and phenylephrine spray and local pressure control the problem. Also suspect cocaine abuse (with septal perforation) or juvenile nasopharyngeal angiofibroma. Posterior packing may be needed for the former, and surgical resection is mandatory for the latter (the tumor is benign, but it can erode into nearby structures). In the elderly and hypertensive, nosebleeds can be copious and life-threatening. BP control is paramount, and posterior packing is usually required. Sometimes angiographic embolization or surgical ligation of the **external** carotid if angiography is not available is the only way to control the problem.

Dizziness may be caused by inner ear disease or cerebral disease. When the inner ear is the culprit, the patients describe the room spinning around them (vertigo); when the problem is in the brain, the patient is unsteady but the room is perceived to be stable. In the first case **meclizine, Phenergan, or diazepam** may help. In the second case, full neurologic workup is in order.

A 45-year-old woman presents with a large, warm, red mass on the lower side of the face and upper neck. She was recently evaluated and treated by her dentist for a tooth infection. The mass pushes up the floor of the mouth on that side. She is febrile.

An abscess of the floor of the mouth, also known as Ludwig's angina, is a surgical emergency. It needs to be incised and drained like all abscesses, but if it continues to enlarge it could compromise her airway; urgent intubation or tracheostomy may be required.

A 29-year-old woman calls your office reporting that she awoke this morning unable to move one side of her face.

Despite her age, make sure to rule out a CVA with a CT of the head, but this is suggestive of Bell's palsy. Treat with antiviral medication and steroids or watchful waiting.

An 18-year-old boy has epistaxis. He denies picking his nose. No source of anterior bleeding can be seen on physical examination.

In this young age group, this condition is either septal perforation from cocaine abuse or posterior juvenile nasopharyngeal angiofibroma. Septal perforation may need posterior packing. Posterior juvenile nasopharyngeal angiofibroma needs to be removed surgically (it is benign but can locally invade other structures).

A 72-year-old man on a baby aspirin with hypertension and diabetes presents to the ED with headaches. Blood pressure is 220/115 mm Hg. He acutely develops severe epistaxis.

This is clearly epistaxis secondary to hypertension. Significant blood can be lost. Pharmacological management of hypertension is obviously needed, but urgent control is necessary—usually with posterior packing. Rarely, emergency arterial ligation or angiographic embolization is necessary.

Neurosurgery 8

Learning Objectives

- ❑ List the differential diagnoses for common presenting complaints
- ❑ Describe treatment options for cerebrovascular occlusive disease
- ❑ Describe primary and metastatic brain tumors, treatment options, and prognosis
- ❑ Provide an approach to treating chronic pain syndromes

The timetable and mode of presentation of neurologic diseases provide the first clues to etiology:

- **Vascular problems** have sudden onset without headache when they are occlusive and with very severe headache when they are hemorrhagic.
- **Brain tumors** have a timetable of months, and produce constant, progressive, severe headache, sometimes worse in the mornings. As intracranial pressure increases, blurred vision and vomiting occur. Focal deficits may be anatomically based.
- **Infectious problems** have a timetable of days or weeks, and often an identifiable source of infection in the history.
- **Metabolic problems** develop rapidly (hours or days) and affect the entire CNS.
- **Degenerative diseases** usually have a timetable of years.

VASCULAR OCCLUSIVE DISEASE

Transient ischemic attack (TIA) is sudden, transitory loss of neurologic function that comes on without headache. It resolves spontaneously within 24 hours without leaving permanent neurologic sequelae.

Symptoms depend on the area of the brain affected, which is related to the vessels involved. The most common origin is high-grade stenosis (≥70%) of the internal carotid or ulcerated plaque at the common carotid bifurcation. TIAs are predictors of stroke, and timely recognition and management can minimize that potential. Workup starts with noninvasive duplex U/S studies.

Treatment is antiplatelet therapy and possible carotid endarterectomy if the lesions are found in a location that explains the neurologic symptoms. In high-risk surgical patients, angioplasty and endovascular stent placement has had some success.

Ischemic stroke also has sudden onset without headache, but in contrast to a TIA the neurologic deficits are present >24 hours and often leave permanent sequelae.

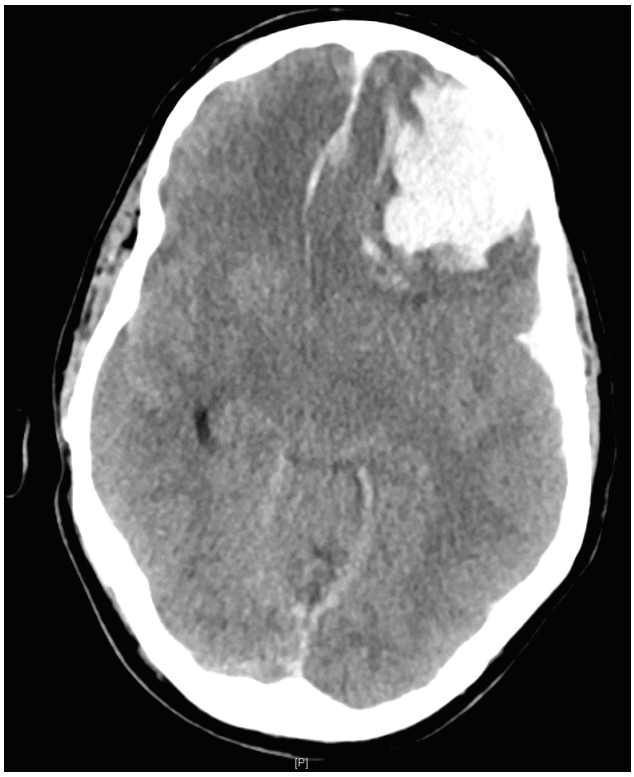
- Very early ischemic stroke (<3 hours) may be amenable to IV tissue plasminogen activator (tPA) or endovascular thrombectomy, but most strokes are not amenable to revascularization.
- Furthermore, an ischemic infarct may be complicated by a hemorrhagic infarct if blood supply to the brain is suddenly increased.
- Vascular workup will eventually be done to identify lesions that might produce another stroke (and treat them), but for the existing infarct, assessment is CT and treatment is rehabilitation.

Intracranial Bleeding

Hemorrhagic stroke is seen in the uncontrolled hypertensive who complains of very severe headache of sudden onset and goes on to develop severe neurologic deficits. CT is used to evaluate the location and extent of the hemorrhage, and treatment is directed at control of the hypertension and rehabilitation efforts.

Subarachnoid hemorrhage can be caused by rupture of an intracranial aneurysm, trauma, or spontaneous bleeding. The amount of pressure that the free blood exerts on the brain determines the severity of symptoms and resultant outcome.

- If there is significant pressure exertion (especially when caused by an aneurysm), patients complain of severe, sudden onset headache, "the worst of their life." Physical exam can demonstrate nuchal rigidity due to meningeal irritation. Testing includes CT and possible MRA or formal angiogram to identify the neurovascular anatomy. Treatment for a cerebral aneurysm is open clipping of the aneurysm or endovascular coiling (both have good results).
- If there is limited bleeding from an aneurysm, there may be only minimal pressure exerted on the brain; symptoms may not appear until 7–10 days after the "sentinel bleed." When that happens, the degree of intracranial hematoma is often significant, and patients cannot always be helped. Therefore, a very high index of suspicion at initial presentation can be lifesaving.



Courtesy of Gary Schwartz, MD

Figure 8-1. Subarachnoid Hemorrhage

A 62-year-old right-handed man has transient episodes of weakness in the right hand, blurred vision, and difficulty expressing himself. There is no associated headache, and the episodes have sudden onset, lasting 5–10 minutes and resolving spontaneously with no neurological sequela.

This scenario is most consistent with TIA in the territory of the left carotid artery caused by stenosis or an ulcerated plaque at the left carotid bifurcation. Start workup with duplex scan. If stenosis exceeds 70%, proceed to carotid endarterectomy.

A 61-year-old man presents with a 1-year history of episodes of vertigo, diplopia, blurred vision, dysarthria, and instability of gait. The episodes have sudden onset, last several minutes, have no associated headache, and leave no neurologic sequela.

This is another version of TIA, but now the vertebral arteries may be involved. Start with duplex scan.

A 60-year-old diabetic man presents to the ED after abruptly developing right-sided hemiparesis 6 hours ago. There was no associated headache and he is alert, but the neurologic deficits have not resolved.

Neurologic catastrophes that begin suddenly and have no associated headache are vascular occlusive in origin. This patient needs a CT to assess the extent of the infarct and supportive treatment with emphasis on rehabilitation. Eventually his neck vessels will be looked at by duplex scan to see whether a second stroke elsewhere may be preventable.

If the vignette had described a patient much earlier in presentation, IV infusion of tissue-type plasminogen activator (tPA) could be started within 90 minutes of the onset of symptoms.

A 39-year-old woman presents to the ED with a history of a severe headache of sudden onset that she says is different and worse than any headache she has ever had before. Her neurologic examination is completely normal, so she is given pain medication and sent home. She improves over the next few days, but 10 days after the initial visit she again gets a sudden, severe, and singular diffuse headache and returns to the ED. This time she has some nuchal rigidity on physical exam.

This is a classic and commonly tested scenario: a subarachnoid bleeding from an intracranial aneurysm. The "sentinel bleed" that is not identified is a common feature; the "sudden, severe, and singular" nature of the pain is also very common. The nuchal rigidity betrays the presence of blood in the subarachnoid space. We are looking for blood inside the head, thus start with CT. Angiograms will eventually follow, in preparation for surgery to clip the aneurysm or endovascular coiling.

BRAIN TUMORS

Brain tumor may present with focal deficits based on location but may be vague:

- Progressively increasing headache for several months
- Worse in the mornings
- Eventual signs of increased intracranial pressure (blurry vision, papilledema, and vomiting)
- Bradycardia and hypertension due to the Cushing reflex

Brain tumor can be visualized very well on CT scan, but MRI gives better detail and is the preferred study. While awaiting surgical removal, treat any increased intracranial pressure with high-dose steroids (e.g., dexamethasone).

Clinical localization of brain tumors may be possible:

- Motor and speech centers are often affected in tumors that press on the lateral side of the brain, producing symptoms on the opposite side of the body.
- **Tumor at the base of the frontal lobe** produces inappropriate behavior, optic nerve atrophy on the side of the tumor, papilledema on the other side, and anosmia (Foster-Kennedy syndrome).
- **Craniopharyngioma** occurs in children who are short for their age; they show bitemporal hemianopsia and a calcified lesion above the sella on x-rays.

- **Prolactinomas** produce amenorrhea and galactorrhea in young women. Diagnostic workup includes ruling out pregnancy and hypothyroidism, determination of prolactin level, and MRI of the sella. Treatment is bromocriptine. Transnasal, transsphenoidal surgical removal is reserved for those who do not respond or those who wish to get pregnant.
- **Acromegaly** develops from the effects of excess growth hormone from a pituitary tumor. It is recognized by the height and the presence of large hands, feet, tongue, and jaws. Additionally, there is hypertension, diabetes, sweaty hands, headache, and the history of wedding bands or hats that no longer fit. Check serum somatomedin C levels and perform an MRI. Treatment is surgical removal, but radiation is an option.
- **Pituitary apoplexy** occurs when there is bleeding into a pituitary tumor, with subsequent destruction of the pituitary gland. The history may have clues to the longstanding presence of a pituitary tumor (headache, visual loss, endocrine problems). The acute episode starts with a severe headache, followed by signs of increased compression of nearby structures by the hematoma (deterioration of remaining vision, bilateral pallor of the optic nerves) and pituitary destruction (stupor and hypotension). Steroid replacement is urgently needed, and eventually other hormones will need to be replaced. MRI or CT will delineate the extent of the problem.
- **Tumor of the pineal gland** produces loss of upper gaze and the physical finding known as "sunset eyes" (Parinaud syndrome).
- **Brain tumor in children** is most commonly in the posterior fossa. It produces cerebellar symptoms (stumbling around, truncal ataxia), and children often assume the knee-chest position to relieve their headache.

Brain abscess present with many of the same manifestations of brain tumor, as it is a space-occupying lesion. However, brain abscess develops more quickly (1–2 weeks). There is fever, and usually an obvious source of the infection nearby, such as otitis media or mastoiditis. It has a very typical appearance on CT; thus the more expensive MRI is not needed. Surgical resection is required.

> A 31-year-old nursing student presents with persistent headaches of increasing intensity that began 4 months ago. They are worse in the mornings. For the past 3 weeks she has been having occasional vomiting. Thinking that she may need new glasses, she sees her optometrist, who discovers that she has bilateral papilledema.

The insidious pattern of progressive symptoms over months is suspicious for a brain tumor. Start with a CT scan, but most likely an MRI will be necessary. Employ measures to decrease ICP while awaiting surgery, including high-dose steroids.

> A 42-year-old right-handed man has had a history of progressive speech difficulties and right hemiparesis for 5 months. He has had progressively severe headaches for the last 2 months. At the time of admission he is confused and vomiting and has blurred vision, papilledema, and diplopia. Shortly thereafter his blood pressure rises to 190/100 mm Hg, and he develops bradycardia.

Another presentation of a brain tumor, but with localizing signs (left parietal and temporal) and presenting with the Cushing reflex due to high ICP. Manage as above, but as an emergency.

A 23-year-old nun presents with a history of amenorrhea and galactorrhea of 6 months' duration. She is very concerned that others might think that she is pregnant, and she vehemently denies such a possibility.

When suspecting a prolactinoma, first confirm that the patient is not pregnant or hypothyroid. Check a prolactin level and perform an MRI. Treatment is bromocriptine. Surgery is reserved for those who do not respond or those who wish to become pregnant.

A 44-year-old man is referred for treatment of hypertension. His physical appearance is impressive: he has big, fat, sweaty hands; large jaw and thick lips; a large tongue; and huge feet. He is also found to have a touch of diabetes. In further questioning he admits to headaches and relates that his wedding ring no longer fits his finger.

There are the hallmark features of acromegaly, which will typically present on the exam with some of these features and potentially an image (hands, jaw). Measure serum somatomedin C level; then perform an MRI and eventually pituitary surgery or radiation therapy.

A 15-year-old girl has gained weight and developed acne and facial hair. She has mild diabetes and hypertension.

Some variant of Cushing syndrome will be presented on the exam, often with "before" and "after" pictures. Management is as described in the endocrine section: an overnight low-dose dexamethasone suppression test and if no suppression, 24-hour urinary cortisol. If cortisol is high, do a high-dose dexamethasone suppression test. If she suppresses at high dose, do an MRI of the sella and follow with transsphenoidal pituitary surgery.

A 27-year-old woman develops a severe headache of sudden onset, making her stuporous. She is taken to the hospital, where she is found to have blood pressure 75/45 mm Hg. Relatives indicate that for the past 6 months she has been complaining of morning headaches, loss of peripheral vision, and amenorrhea.

This scenario is most consistent with pituitary apoplexy—she has bled into a pituitary tumor. Steroid replacement is urgently needed. Other hormones will need to be replaced eventually. MRI or CT will determine extent of the problem.

A 6-year-old boy has been stumbling around the house and complaining of severe morning headaches for the past several months. While waiting in the office to be seen, he assumes the knee-chest position as he holds his head. Neurologic examination demonstrates truncal ataxia.

Brain tumors in children typically occur in the posterior fossa, affecting cerebellar function. MRI and neurosurgery are required.

A 23-year-old man develops severe headaches, seizures, and projectile vomiting over a period of 2 weeks. He has low-grade fever and was recently treated for mastoiditis.

The short interval of presentation and recent infection as suggestive of a brain abscess. Start with a CT; management is surgical.

PAIN SYNDROMES

Pain syndromes are very difficult to diagnose and manage. Other etiologies must be satisfactorily ruled out prior to diagnosing a chronic pain condition.

Trigeminal neuralgia (**tic douloureux**) produces extremely severe, sharp shooting or burning pain in the face in the distribution of the trigeminal nerve. Patients often describe the pain as a "bolt of lightning" brought about by touching a specific area and lasting 60 seconds. Patients, typically elderly, have a completely normal neurologic exam. The only finding on physical exam may be an unshaven area in the face (the trigger zone, which the patient avoids touching). MRI is done to rule out organic lesions. Treatment with anticonvulsants is often successful. If not, radiofrequency ablation can be done.

Reflex sympathetic dystrophy (**causalgia**) develops several months after peripheral nerve injury (e.g., crush injury of nerve). There is constant, burning, agonizing pain that does not respond to the usual analgesics. The pain is aggravated by the slightest stimulation of the area. The extremity is cold, cyanotic, and moist. A successful sympathetic block is diagnostic, and surgical sympathectomy is curative.

Organ Transplantation 9

Learning Objectives

- ❑ Describe the policies related to waiting lists for organ transplantation
- ❑ Describe the common complications in organ transplantation

DONOR SELECTION

The selection of donors for transplant has been liberalized in order to alleviate the acute shortage of organs, with improving results. The general rule is that all potential donors are referred to the United Network for Organ Sharing (UNOS), and they will exclude the rare donors that cannot be used at all.

- Virtually all brain-dead patients are potential candidates, regardless of age.
- Some donors with specific infections (e.g., hepatitis) can be used for recipients who have the same underlying infection.
- Even donors with metastatic cancer can donate corneas, because the cornea does not have a blood supply.

Historically, infectious diseases such as hepatitis and HIV were considered absolute contraindications to organ transplantation. This has recently changed:

- Seropositive organs are now being transplanted to seropositive recipients.
- Hepatitis can now be pharmacologically cured, allowing for transplantation into seronegative recipients with subsequent treatment.

TRANSPLANT REJECTION

After an organ has been transplanted, rejection can develop despite immunosuppressive medications. Tissue typing and a close tissue match may minimize that risk, but it is an ever-present concern for most patients.

Transplant rejection can occur in 3 ways: hyperacute, acute, or chronic.

Hyperacute Rejection

Hyperacute rejection is a vascular thrombosis that occurs within minutes of reestablishing blood supply to the organ. It is caused by preformed antibodies. It is preventable by ABO matching and lymphocytotoxic crossmatch; therefore it is rarely seen clinically.

Acute Rejection

Acute rejection (most common) often occurs after the first 5 days but always within the first 3 months. Episodes occur even if the patient is on maintenance immunosuppression.

Signs of organ dysfunction suggest it, and biopsy confirms it.

- **Liver**: Technical problems are more commonly encountered than immunologic rejection. Thus, the initial priorities if liver function deteriorates post-transplant (rising gamma-glutamyl transferase [GGT], alkaline phosphatase, and bilirubin) are to rule out biliary obstruction by U/S and vascular thrombosis by Doppler study.
- **Heart**: Signs of functional deterioration occur too late to allow effective treatment, so routine myocardial biopsy (percutaneously via the jugular vein) is done at set intervals. First-line treatment for acute rejection is high-dose steroids. If unsuccessful, antilymphocyte agents have been used, though their high toxicity is a problem. Newer anti-thymocyte serum is tolerated better. Efforts are underway to utilize MRI as a non-invasive way to diagnose rejection without the need for biopsy. Rarely, retransplantation is necessary.
- **Lung**: Worsening dyspnea and the need for oxygen supplementation should prompt chest x-ray, CT scan, and ultimately transbronchial biopsy. Treat as with heart transplant rejection.

Chronic Rejection

Chronic rejection is seen years after the transplant, with gradual, insidious loss of organ function. It is poorly understood and irreversible. Although there is no treatment, the transplant can be biopsied in the hope that it may be a delayed (and treatable) case of acute rejection. Occasionally, retransplantation is necessary.

> A 62-year-old man who had a motorcycle accident has been in a coma for several weeks. He is on a respirator, has had pneumonia on and off, has been on vasopressors, and shows no signs of neurologic improvement. The family inquires about brain death and possible organ donation.

All patients that are moribund should be considered for organ donation. Neurological reflex exam, apnea testing, and cerebral blood flow studies are all utilized to establish brain death. Age cutoffs for donation are organ-specific. Infectious diseases such as hepatitis and HIV are no longer absolute contraindications to organ transplantation.

> Ten days after liver transplantation, alkaline phosphatase and bilirubin are noted to be increasing. The patient is asymptomatic.

So early after a transplant, this scenario is concerning for a technical problem versus acute rejection. Do an U/S; if a technical problem exists, surgical or endoscopic interventions may salvage the organ. If absent, immunomodulation is necessary, typically starting with a steroid bolus.

On week 3 after a closely matched renal transplant, there are early clinical and lab signs of decreased renal function.

This is likely acute rejection requiring immunomodulation. If a technical problem existed it would be expected earlier, but assess arterial and venous patency with U/S.

Two weeks after a lung transplant, the patient develops fever, dyspnea, hypoxemia, decreased FEV1, and interstitial infiltrates on chest x-ray.

This is likely acute rejection, but an infectious etiology must also be considered. Treatment is antibiotics and possible antifungal therapy, as lung transplants are prone to fungal infection. Bronchoscopy with bronchoalveolar lavage is diagnostic, but patients may not tolerate without intubation. Transbronchial biopsy may be needed to establish a diagnosis of rejection, but given the need to intubation, empiric immunosuppression is often administered once an infectious etiology has been ruled out or treated.

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